Editorial

Thus did John Milton in *Paradise Lost* (1667) describe Satan when the guards found him in the Garden of Eden assaying to raise in Eve "vain hopes, vain aims, inordinate desires blown up with high conceits ingendering (sic) pride" (1). Milton portrayed Eve as a sought after but attainable prize through whom Satan hoped to seduce Adam into eating the forbidden fruit granting knowledge of good and evil. In this issue, Zhu et al. (2) describe the molecular biology of an endogenous vascular elastase which they have cleverly dubbed EVE. The acronym is well chosen as like Eve, "the mother of all living things" (Gen. 3:20), EVE not only has an essential role in initiating pulmonary vascular remodeling, but also represents an attainable link to understanding this complex and often out of control process involving thickening of the existing media with extension into more distal precapillary vessels often further narrowing the lumen. This EVE may also be integral to the deremodeling of the exuberant vascular growth of the fetus, which if unresolved may result in the sometimes lethal persistent pulmonary hypertension of the newborn.

Chronic hypoxia, as occurs at altitude or in patients with cystic fibrosis or chronic obstructive lung disease, is the most common cause of pulmonary hypertension and vascular remodeling. Hypoxia causes an acute lung vasoconsriction which has been thought to initiate the remodeling either directly or by secondarily raising pressure in the vessels. However, the relationship between acute hypoxic vasoconstriction and vascular remodeling is not perfect, and the act of squeezing may not be the cause of the remodeling. Perhaps hypoxia itself or shear stress on the endothelium or a change in endothelial permeability initiates the changes. In this regard, Dr. Rabinovitch's laboratory has shown that inhibitors of elastase can prevent the pulmonary vascular remodeling not only in monocrotaline-injected rats, in which they have characterized EVE, but in rats exposed to chronic hypoxia (3). In the monocrotaline rats it is easy to envision that this toxin causes vascular wall damage, and the ensuing response, including activation of an elastase, may all be the vessel's response to injury as it seeks to contain the wound. This mechanism could explain the rare human condition of primary pulmonary hypertension in which the remodeling is a response to some yet to be identified agent. However, it is intriguing to think that EVE may regulate the much more prevalent condition of chronic hypoxic pulmonary hypertension either as an initiating factor or as a contributor to the vascular architectural changes.

Elastin, which is EVE's substrate, occurs as an internal and external elastic lamina and in more proximal vessels as multiple concentric layers in the media where it has a major role in tissue recoil (4). The internal elastic lamina also is a selective barrier to passage of large molecules such as low density lipoprotein but more porous to smaller molecules like albumin. Elastin peptides are chemotactic for fibroblasts and monocytes. Which of these aspects of elastin, if any, are important in the mechanism by which EVE influences vascular architectural changes is unknown.

The characterization of EVE, which is closely related to the serine proteinase adipsin, and thus to complement factor D, has important implications both for the treatment and understanding of pulmonary hypertension and systemic vascular disease. To date EVE has only been shown convincingly in proximal pulmonary arteries which do remodel in rats, but much less so in humans. Failure to show EVE in peripheral vessels, where most of the remodeling occurs, however, is probably a technical problem related to the increased background activity in the lung parenchyma around the more peripheral vessels which may obscure the recognition of EVE. The hypothesis that release of EVE can activate growth factors and consequently stimulate connective tissue protein synthesis and cell changes arises from work from this and other laboratories and is outlined in the paper. Upregulation of EVE or a similar enzyme has also been observed in coronary arteries in association with the development of the post-cardiac transplant arteriopathy, so it would be interesting to determine whether this enzyme plays an important pathophysiologic role in neointimal proliferation in systemic arteries as it may in pulmonary vascular remodeling (5). Other investigators have shown that collagenases, metalloproteinases as well as plasminogen activator, are expressed in carotid arteries of rats after balloon denudation injury (6). Thus, it would be interesting to evaluate the role of EVE relative to these other enzymes. The EVE of the lung vessels which aids in the resolution of fetal remodeling may not be identical to the EVE of the systemic vessels. If systemic and lung EVE are the same, then this enzyme may well mediate the vascular remodeling of systemic hypertension or be the cause of the elastolytic activity found in the walls of aneurysms, perhaps the systemic equivalent of the plexiform lesion which is characteristic of some forms of primary pulmonary hypertension (7).

Other questions are raised. Does EVE have an endogenous vascular elastase inhibitor? This question is particularly relevant to the balance of forces that promote and oppose remodeling in the vessel as EVE is present only in actively remodeling vessels. Chronic hypoxia in the adult animal or human produces an increase in pulmonary artery pressure and vascular remodeling which stabilizes (8). Consequently, it is rare to see a mean pulmonary artery pressure over 45 mmHg in patients with advanced chronic obstructive lung disease. In contrast, neonatal animals exposed to chronic hypoxia or patients with primary pulmonary hypertension develop progressive remodeling of the pulmonary vessels until death (9). What controls EVE in these two settings? Is there an EVE inhibitor? Thus EVE, like her namesake, provides us with questions and enigmas. Does it all begin with EVE when it comes to systemic and pulmonary vascular remodeling?

Charles A. Hales
Department of Medicine
Pulmonary and Critical Care
Massachusetts General Hospital
and Harvard Medical School

J. Clin. Invest.

0021-9738/94/09/0919/02 $2.00
Volume 94, September 1994, 919–920

References

1. Milton, J. 1952. Paradise Lost. Encyclopaedia Britannica Inc. Chicago. 412 pp.

2. Zhu, L., D. Wigle, A. Hinek, J. Kobayashi, C. Ye, M. Zuker, H. Dodo, F. W. Keeley, and M. Rabinovitch. 1994. The endogenous vascular elastase which governs development and progression of monocrotaline-induced pulmonary hypertension in rats is a novel enzyme related to the serine proteinase adipsin. *J. Clin. Invest.* 94:1163–1171.

3. Maruyama, K., Y. Chongliang, M. Woo, H. Venkatacharya, L. Lines, M. Silver, and M. Rabinovitch. 1991. Chronic hypoxic pulmonary hypertension in rats and increased elastolytic activity. *Am. J. Physiol.* 261:H1716–H1726.

4. Rosenbloom, J., W. R. Abrams, and R. Mecham. 1993. Extracellular matrix 4: the elastic fiber. *FASEB (Fed. Am. Soc. Exp. Biol.) J.* 7:1208–1218.

5. Oho, S., and M. Rabinovitch. 1994. Post-cardiac transplant arteriopathy in piglets is associated with fragmentation of elastin and increased activity of a serine elastase. *Am. J. Pathol.* 145:202–210.

6. Jackson, C. L., E. W. Raines, R. Ross, and M. A. Reidy. 1992. Role of plasminogen activation in smooth muscle cell migration after arterial injury. *Ann. NY Acad. Sci.* 667:141–150.

7. Derouette, S., W. Hornebeck, D. Loisance, G. Godeau, J. P. Cachera, and L. Robert. 1981. Studies on elastic tissue of aorta in aortic dissections and Marfans syndrome. *Pathol. Biol.* 29:539–545.

8. Thompson, B. T., D. M. Steigman, C. L. Spence, S. P. Janssens, and C. A. Hales. 1993. Chronic hypoxic pulmonary hypertension in the guinea pig: effect of three levels of hypoxia. *J. Appl. Physiol.* 74:916–921.

9. Botney, M. D., W. C. Parks, E. C. Crouch, K. Stenmark, and R. P. Mecham. 1992. Transforming growth factor-β_1 is decreased in remodeling hypertensive bovine pulmonary arteries. *J. Clin. Invest.* 89:1629–1635.