INTRODUCTION

The endothelium is a single layer of cells lining blood and lymphatic vessels. The endothelium separates the contents of the lumen of blood vessels from the underlying connective tissue and vascular smooth muscle. It therefore serves as a semi-permeable barrier, regulating the movement of substances from the lumen of the blood vessel to the interstitium, and vice-versa. The endothelium also acts as a transducer of signals from the lumen to the vascular smooth muscle, and plays a crucial role in regulating inflammatory responses and regulating the growth of new blood vessels. Nitric oxide (NO) is produced via the metabolism of L-arginine by a family of enzymes known as nitric oxide synthases (NOS). Endothelial NO production occurs primarily via the appropriately named endothelial NOS (eNOS). In recent years a great deal has been learned about the molecular regulation of eNOS activity. Moreover, the availability of selective NOS inhibitors and of genetically modified mice that lack eNOS has aided in gaining a better understanding of the physiological and pathophysiological roles of eNOS. NO is an important regulator of blood pressure and of local tissue blood flow. Along with prostacyclin, endothelial NO production is crucial to the regulation of platelet aggregation, as well as in regulating leukocyte adherence to endothelium (thus modulating inflammatory responses). In situations of endothelial dysfunction the impairment of NO synthesis contributes to elevated blood pressure, enhanced inflammatory reactions, impaired tissue blood flow and thrombogenesis. Controlled delivery of NO from exogenous sources may represent an attractive approach to the treatment of disorders characterized by endothelial dysfunction.

As in many tissues, the actions of NO on endothelial function can appear to be inconsistent, causing stimulation of a function in some instances and inhibition of the same function in other instances. Usually these differences are related to the concentration of NO produced. This chapter is focused on the physiological effects of NO (generated by eNOS), rather than the pathophysiological effects associated with high concentrations of NO.
PORTAL HYPERTENSION IN THE 21ST CENTURY

THE ENDOTHELIUM AS A BARRIER

Throughout the body the endothelium acts as a barrier to restrict movement of materials between the interstitium and the lumen of blood vessels. The regulation of the permeability of this barrier can be crucial for survival of an organism. For example, the “blood–brain barrier” consists of the endothelial cells in the brain that restrict movement of potentially noxious blood-borne substances from gaining entry to the central nervous system. The permeability of the blood–brain barrier is, at least in part, regulated by NO.

Endothelial permeability is regulated by contractile elements within these cells. Contraction of these elements opens the gaps between neighboring cells, facilitating the movement of fluid or cells between the lumen and the interstitium. Thus, endothelial contraction contributes to edema formation in the context of inflammation. Various chemical mediators can increase endothelial permeability and promote edema formation, including histamine, leukotriene C₄ and platelet-activating factor. NO, in physiological concentrations, acts to diminish endothelial permeability (i.e. an anti-inflammatory action). Moreover, NO donors have been found to reduce edema formation in various experimental models, while inhibitors of NO synthesis can exacerbate edema formation.

THE ENDOTHELIUM AS A TRANSDUCER

In 1980 Furchgott and Zawadzki reported the existence of what they termed an “endothelium-derived relaxing factor” or “EDRF”. It had been known for many years that acetylcholine caused relaxation of vascular smooth muscle. What Furchgott and Zawadzki demonstrated was that, if they removed the endothelium from their blood vessel preparations, acetylcholine could no longer produce a relaxation of the vascular smooth muscle. They proposed that acetylcholine stimulated the production by the endothelium of a substance (EDRF) that diffused to the adjacent vascular smooth muscle where it induced relaxation. This stimulated a vigorous race among cardiovascular physiologists and pharmacologists for the identification of EDRF. At a conference on EDRF in 1986, Louis Ignarro and Robert Furchgott independently proposed that EDRF was NO, and in the following year, Ignarro et al. and Palmer et al. independently demonstrated that this was indeed the case. Furchgott and Ignarro received the Nobel Prize for Medicine/Physiology in 1998 for their pioneering work on the biology of EDRF and NO.

It is now recognized that many vasodilators produce their effects via stimulation of NO synthesis by the endothelium, including histamine, calcitonin gene-related peptide and bradykinin. These mediators bind to specific receptors on the luminal surface of endothelial cells and trigger the activation of eNOS (discussed in more detail below). This enzyme converts L-arginine plus oxygen to L-citrulline plus NO. The NO is able to freely diffuse from the endothelial cells. From the basolateral side of the endothelial cell NO can diffuse to the neighboring smooth muscle cells, where it can bind to and