0031-6997/95/4701-0087$03.00/0
PHARMACOLOGICAL REVIEWS
Vol. 47, No. 1

Printed in U.S.A.

Regulation of Pulmonary Vascular Tone

PETER J. BARNES* AND SHU FANG LIU

Department of Thoracic Medicine, National Heart and Lung Institute, London, UK

* To whom correspondence should be addressed: Professor P. J. Barnes, Department of Thoracic Medicine, National Heart and Lung Institute, Dovehouse Street, London SW3 6LY, UK.

I. Introduction

The normal adult pulmonary circulation is a low-pressure, low-resistance circuit that accommodates the whole output of the right ventricle to the gas exchanging surface at less than 20% of the systemic pressure. Vasodilators normally have little or no effect on pulmonary vascular pressures, indicating that there is little or no resting tone. In contrast to the systemic circulation, where neural and humoral mechanisms predominate, the pulmonary circulation is under the control of both active and passive factors (Daly and Hebb, 1966). Active factors alter pulmonary vascular resistance and tone by causing contraction or relaxation of vascular smooth muscle. These factors include autonomic nerves, humoral factors, and gasses. Passive factors include changes in cardiac output, left atrial pressure, airway and interstitial pressure, gravitational force, and vascular obstruction or recruitment. Passive factors change pulmonary vascular resistance and/or blood flow independently of the changes in vascular tone. Although passive factors may be important in some circumstances, the pulmonary circulation is acknowledged to be under active control, and this may be particularly relevant in disease (Barer, 1980).

This review describes the current understanding of the active control of pulmonary circulation. Our knowledge of the control of human pulmonary vessels is far from complete, and it is important to recognize that there are marked differences in pulmonary vascular responses between species. This may relate to alterations in structure, in expression of receptors, and in coupling of receptor mechanisms to responses. There are also changes during development, particularly at birth, as the fetal lungs adapt to air breathing (Howarth and Hislop, 1981).

A. Structure of Pulmonary Vessels

Pulmonary arteries, in contrast to systemic arteries, have a much thinner smooth muscle layer under normal

conditions, consistent with a low-pressure system. Small pulmonary arteries of several hundred μm internal diameter are the major site of vascular resistance and are the site of HPV.† The pulmonary capillary bed responds differently from the systemic capillary bed. Pulmonary veins are similar in structure to pulmonary arteries but have less smooth muscle and may be regulated differently. Constriction of pulmonary arteries results in elevated pulmonary artery pressure, which increases the pressure on the right side of the heart, whereas constriction of pulmonary veins increases pulmonary capillary pressure, and this could result in pulmonary edema.

With disease, the structure of pulmonary vessels may change markedly. With a chronic increase in pulmonary vascular pressure, there is a structural remodelling with fibrosis, particularly in the intimal layer, and increased size of the smooth muscle layer. This may result in a marked alteration in control mechanisms.

B. Role of Endothelium

As in the systemic circulation, endothelial cells in the pulmonary circulation have a profound influence on vascular tone. Endothelial cells have the capacity to release several constrictor and dilator substances, as well as agents that affect the growth and differentiation of cells in the vessel wall (Liu and Barnes, 1994). When discussing the actions of drugs on pulmonary vessels, it is important to consider their effects on the endothelium and on pulmonary vascular smooth muscle cells, inasmuch as many agonists influence pulmonary vascular tone via the release of endothelial mediators (fig. 1).

II. Neural Mechanisms

The autonomic nervous system may modify pulmonary blood flow under physiological conditions and may be involved in the pathophysiology of pulmonary vascular diseases. Our understanding of autonomic control mechanisms has increased greatly in recent years, with (*a*) the identification of novel neurotransmitters such as neuropeptides, purines, and NO, (*b*) the recognition of multiple autonomic receptor subtypes, and (*c*) the demonstration of multiple prejunctional control mechanisms in autonomic nerve endings. Pulmonary vascular tone is regulated by many autonomic receptors (table 1).

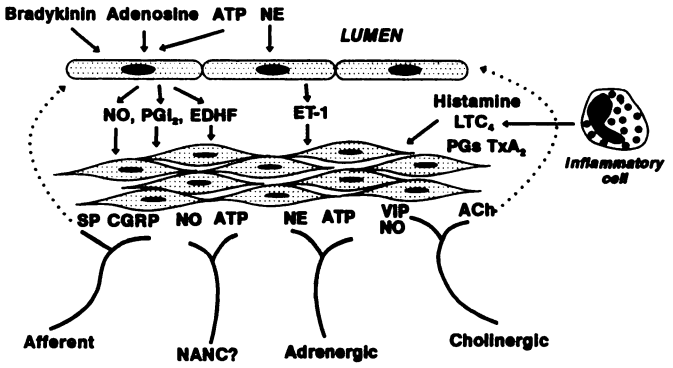

FIG. 1. Regulation of pulmonary vascular tone. Pulmonary vascular tone is regulated by autonomic nerves, and mediators from inflammatory cells and endothelial cells.

A. Adrenergic Mechanisms

1. Adrenergic innervation. Sympathetic nerves supplying the pulmonary vessels arise from nerve cell bodies in the first five thoracic ganglia, the satellite ganglia, and middle and inferior cervical ganglia (Daly and Hebb, 1966; Richardson, 1979). Postganglionic fibers from these ganglia intermingle with parasympathetic nerve fibers to form anterior and posterior plexi at the tracheal bifurcation (Daly and Hebb, 1966). Nerve fibers arising from these plexi enter the lungs to form a periarterial plexus, which innervates the pulmonary vascular tree, and a peribronchial plexus, which innervates the bronchial tree. There are extensive connections between these plexi (Richardson, 1979). The periarterial plexus starts as bundles of large nerve trunks, but these diminish in size so that at the level of arterioles, there is only a single fiber (Richardson, 1979).

TABLE 1
Autonomic receptors in pulmonary vessels

Receptors	Subtype	Responses	Endothelium dependency
Adrenergic	α_1	contraction	no
	α_2	relaxation	yes
	β_2	relaxation	yes
Muscarinic	M_3	relaxation	yes
Purinergic	P_{2x}	contraction	no
	P_{2y}	relaxation	yes
Tachykinin	NK_1	relaxation	yes
	NK_2	contraction	no
VIP	?	relaxation	yes or no
CGRP	?	relaxation	no

† Abbreviations: HPV, hypoxic pulmonary vasoconstriction; NO, nitric oxide; PPA, pulmonary arterial pressure; AChE, acetylcholinesterase; ACh, acetylcholine; NANC, nonadrenergic, noncholinergic; i-NANC, inhibitory nonadrenergic, noncholinergic; EFS, electrical field stimulation; ATP, adenosine triphosphate; VIP, vasoactive intestinal polypeptide; SP, substance P; CGRP, calcitonin gene-related peptide; L-NMMA, N^G-monomethyl L-arginine; L-NAME, N^G-L-arginine methyester; cGMP, cyclic guanosine 3′, 5′ monophosphate; PVR, pulmonary vascular resistance; A-II, angiotensin-II; NPY, neuropeptide Y; ANP, atrial natriuretic peptide; BK, bradykinin; AVP, arginine vasopressin; PACAP, pituitary adenylate cyclase activating peptide; PG, prostaglandin; ADP, adenosine diphosphate; AMP, adenosine monophosphate; 5-HT, 5-hydroxytryptamine; PAF, platelet-activating factor; DNA, deoxyribonucleic acid; BNP, brain natriuretic peptide; CNP, C-type natriuretic peptide; mRNA, messenger ribonucleic acid; ARDS, adult respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; Ca, calcium; ET, endothelin; cAMP, cyclic adenosine 3′, 5′ monophosphate; NK, neurokinin; NP, neuropeptide; H, histamine; LT, leukotriene; Tx, thromboxane; iNOS, inducible nitric oxide synthase; TNF-α, tumor necrosis factor-α; eNOS, endothelial nitric oxide synthase; HPH, hypoxia-induced (secondary) pulmonary hypertension; EDRF, endothelium-derived relaxing factor; EDHF, endothelium-derived hyperpolarizing factor; L-NA, N^G-nitro-L-arginine; PKC, protein kinase C; PPH, primary pulmonary hypertension; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance.

Histochemical examination reveals that, although the extrapulmonary arteries and veins generally have abundant catecholamine-containing nerve fibers in all species examined so far, the extent and density of the nerve fiber distribution in the intrapulmonary arteries varies considerably between species (Richardson, 1979; McLean, 1986). Catecholamine-containing nerve fibers are generally absent in the intrapulmonary arteries of rat (Bradley et al., 1970; El-Bermani, 1978; McLean et al., 1985), mouse, hedgehog, and badger (Cech, 1969) but are sparsely distributed among intrapulmonary arteries of pig and calf, extending to those arteries larger than 70 μm in diameter (Hebb, 1969). The intrapulmonary arteries of the guinea pig (Kai, 1969), rabbit (Cech and Dolezel, 1967), sheep, cat (Hebb, 1969), and dog (Fillenz, 1970; Kadowitz et al., 1981) have an extensive and dense adrenergic innervation, which extends to the arteries < 70 μm outer diameter. Human intrapulmonary arteries are also intensively innervated with adrenergic nerve fibers extending to arterioles < 60 μm outer diameter (Kai, 1969; McLean, 1986). Human small pulmonary arteries of 100 μm outer diameter still have a surrounding plexus of fluorescent nerve bundles at the adventiomedial margin (Kai, 1969; Mclean, 1986). Compared with pulmonary arteries, intrapulmonary veins are generally more sparsely innervated (Hebb, 1969; Cech, 1969; McLean, 1986).

Ultrastructural studies have confirmed the presence of adrenergic nerve profiles with small dense core vesicles in the intrapulmonary arteries of the cat (Knight et al., 1981; Rhodin, 1978), dog (Fillenz, 1970), and rabbit (McLean, 1986) but not the rat (McLean, 1986). Ultrastructural results correlate well with functional studies. In the intact and perfused pulmonary vascular bed, stimulation of sympathetic nerves to the lung induces a frequency-dependent increase in perfusion pressure and pulmonary vascular resistance. (Kadowitz and Hyman, 1973; Kadowitz et al., 1976), which is blocked by α-adrenoceptor antagonists (Hyman and Kadowitz, 1985) and abolished by the adrenergic neuron blockers guanethidine and bretylium and by chemical denervation with 6-hydroxydopamine (Kadowitz et al., 1975, 1976). Moreover, the attenuated vasoconstrictor response to sympathetic nerve stimulation induced by 6-hydroxydopamine treatment is associated with a marked decrease in the density of fluorescent adrenergic nerve fibers and with ultrastructural changes in the appearance of adrenergic terminal profiles in both intrapulmonary arteries and veins (Kadowitz et al., 1976).

2. Adrenergic receptors. Norepinephrine released from sympathetic nerves and epinephrine secreted by the adrenal medulla act on multiple adrenoceptor subtypes. Three subtypes of β-receptor (β_1-, β_2-, and β_3-) can be distinguished both pharmacologically and at a molecular level. α-Receptors are classified into α_1- and α_2- receptors, which are further classified into α_{1A}-, α_{1B}- and α_{1C}-receptors, and α_{2A}-, α_{2B}-, α_{2C}- and α_{2D}-receptors at a molecular level, although these cannot always be distinguished pharmacologically (Strasser et al., 1992).

Both β_1- and β_2-adrenoceptors have been identified functionally in isolated pulmonary vessel rings and in the pulmonary vascular bed; they mediate vasodilation in response to circulating catecholamines (Boe and Simonsson, 1980; Hyman et al., 1981) and to neurally released norepinephrine (Hyman et al., 1990). As in systemic vessels, these receptors are generally of the β_2-receptor subtype, although this varies between species. Thus, β-adrenoceptors on the pulmonary vessels of guinea pig, rabbit (O'Donnell and Wanstall, 1985), and cat (Hyman et al. 1981, 1990) are exclusively of the β_2-receptor subtype, whereas in the rat, β_2-receptors predominate with a small number of β_1-receptors also present (O'Donnell and Wanstall, 1984; Shaul et al., 1990). Binding studies indicate that the β-adrenoceptors on human pulmonary vessels are β_2-receptors (Carstairs et al., 1985), but functional studies also suggest the presence of β_1-receptors (Boe and Simonsson, 1980). Cultured endothelial cells of bovine (Ahmad et al., 1990) and human (Grigorian et al., 1989) pulmonary arteries have a high density of β-adrenoceptors. These receptors are heterogeneous on the bovine endothelial cells, with 25% of them being of the β_1-receptor subtype and the remaining 75% consisting of β_2- or atypical β-receptors. There are also facilitatory β_2-adrenoceptors on the pulmonary sympathetic nerve endings (Costa and Majewski, 1988; Molderings et al., 1988; Starke et al., 1989); these facilitate the release of norepinephrine.

Less information is available about the distribution of α-adrenoceptors. Studies using selective agonists and antagonists have demonstrated the presence of α_1- and α_2-receptors on isolated pulmonary vessel rings and in the pulmonary vascular bed of the rabbit (Docherty and Starke, 1981), cat (Hyman and Kadowitz, 1985; Hyman et al., 1986), and dog (Greenberg et al., 1981; Shebuski et al., 1986). Both receptors mediate vasoconstriction. Canine pulmonary arteries have been reported to respond only to α_1-adrenoceptor agonists (Shebuski et al., 1987), whereas pulmonary veins constrict to both α_1- and α_2-adrenergic agonists (Ohlstein et al., 1989). These results suggest that α_1-adrenoceptors are located on both pulmonary artery and vein, but α_2-adrenoceptors are to be found only on pulmonary vein. There are also autoregulatory α_2-adrenoceptors on sympathetic nerve endings that participate in a feedback mechanism to modulate norepinephrine release (Starke et al., 1989). Endothelial α_2-adrenoceptors mediating vasodilation through the release of NO have been demonstrated in pulmonary vessels (Liu et al., 1991a; Pepke-Zaba et al., 1993).

3. Adrenergic control of pulmonary vascular tone. Francois-Franck (1896) observed an increase in the pulmonary artery blood pressure and heart rate in response to the stimulation of sympathetic nerves supplying the lung. However, because changes in cardiac output, airway pressure, and other systemic hemodynamic param-

eters that occur during sympathetic nerve stimulation have effects on the PPA and vascular resistance, it was not possible to determine whether the increased pulmonary arterial pressure was attributable to pulmonary vasoconstriction. Daly and colleagues (Daly and Hebb, 1952; Daly and Hebb, 1966; Daly et al., 1970) demonstrated that under conditions of constant flow, sympathetic nerve stimulation consistently increases pulmonary vascular resistance. On the other hand, in an in situ perfused dog lung preparation, sympathetic nerve stimulation has little or no effect on pulmonary vascular resistance but decreases pulmonary vascular compliance (Ingram et al., 1968, 1970). The reason for this discrepancy is unclear but may relate to different basal conditions and surgical manipulations. In a closed-chest dog lung lobe perfused at constant flow, there is a frequency-related increase in pulmonary vascular resistance in response to sympathetic nerve stimulation (Kadowitz and Hyman, 1973). This response is independent of changes in respiration, bronchomotor tone, and blood flow in the bronchial circulation. Sympathetic nerve stimulation may increase pulmonary vascular resistance by up to 70% (Daly and Daly, 1973; Kadowitz et al., 1975). Sympathetic nerve stimulation also increases pulmonary input impedance and pulmonary vascular resistance (Pace et al., 1971; Piene, 1976), indicating that both increases in pulmonary vascular resistance and decreases in pulmonary vascular compliance can be induced by sympathetic nerve stimulation. Thus, sympathetic activation causes an increase in pulmonary vascular resistance and a decrease in pulmonary vascular compliance, thereby increasing PPA.

Both the increase in pulmonary vascular resistance and the decrease in pulmonary vascular compliance that occur during sympathetic nerve stimulation are mediated by α-adrenoceptors (Ingram et al., 1968, 1970; Kadowitz and Hyman, 1973; Kadowitz et al., 1975, 1976), and primarily by α_1-adrenoceptors (Hyman, 1986). There also seems to be a β-adrenoceptor-mediated pulmonary vasodilation in response to sympathetic nerve stimulation inasmuch as in the presence of α-adrenoceptor blockade, sympathetic nerve stimulation elicits a vasodilator response (Hyman et al., 1981), and that β-adrenoceptor blockade enhances the constrictor response to sympathetic nerve stimulation (Hyman, 1986).

Sympathetic nerves may also play a role in the maintenance of basal pulmonary vascular tone. Removal of the satellite ganglia and the first five thoracic sympathetic ganglia significantly decrease pulmonary vascular resistance in cats (Duke and Stedeford, 1960). Thoracic sympathectomy lower PPA and vascular tone in the dogs and lambs (Kabins et al., 1962; Colebatch et al., 1965). Moreover, α-adrenergic antagonists reduce pulmonary vascular resistance in anesthetized cats and conscious dogs (Barer, 1966; Murray et al., 1986), and β-adrenergic antagonists increase pulmonary vascular resistance in anesthetized and conscious dogs and sheep (Malik and Newmark, 1976; Murray et al., 1986; Kane et al., 1994). These results indicate that there is a degree of basal sympathetic tone under normal physiological conditions. After left lung autotransplantation in dogs, there is an increased response to α-adrenergic agonists, presumably attributable to denervation supersensitivity (Nishiwaki et al., 1993). This provides additional evidence of basal adrenergic tone in the pulmonary vascular bed under normal physiological conditions, although this is lower than in the systemic circulation.

The segmental distribution of the vasoconstrictor response to sympathetic nerve stimulation in the pulmonary circulation is not entirely clear. By comparing the responses during forward and retrograde perfusion, Daly et al. (1970) concluded that the arteries were the major site of the increased resistance. Direct measurements of pressure in intrapulmonary veins of 2.5 to 3.5 mm diameter have indicated that up to 50% of the increase in total pulmonary vascular vascular resistance occurs in these vessels (Kadowitz et al., 1975). Using a stop-flow technique, a venous component in the vasoconstrictor response to satellite ganglion stimulation is not apparent, although these vessels constrict to exogenous norepinephrine (Hakim et al., 1979).

B. Cholinergic Mechanisms

1. Cholinergic innervation. Unlike in the airway, where cholinergic innervation predominates (Barnes, 1986), the pulmonary circulation receives less cholinergic input, compared with adrenergic innervation. Preganglionic cholinergic efferent nerve fibers arise from the vagal nuclei of the brainstem and pass down the vagus nerves into the lungs (Daly and Hebb, 1966). These fibers relay in the pulmonary plexi or with the postganglionic nerve cell bodies in hilar plexi. The distribution of these postganglionic nerve fibers along the pulmonary vascular tree has been studied in detail using histochemical techniques, including AChE staining and choline acetyltransferase staining. There is a marked species-dependent variation in the distribution of cholinergic nerve fibers. Intrapulmonary arteries of the guinea pig, mouse, and rat have no AChE-positive nerve fibers, although they were found in the extrapulmonary arteries and large pulmonary veins of these species (Cech, 1969, 1973; Bradley et al., 1970). AChE-positive nerve fibers are found in pig pulmonary arteries larger than 200 μm in diameter and large pulmonary veins (Hebb, 1969). The pulmonary arteries of calf have a sparse cholinergic nerve fiber distribution, which does not extend to vessels < 70 μm in diameter (Hebb, 1969). Pulmonary arteries of the rabbit, dog, monkey, sheep, and cat (Cech, 1969, 1973; Fillenz, 1970) are extensively innervated with AChE-positive nerve fibers. In the rabbit, these extend down to the vessels of < 100 μm (Hebb, 1969) and even to arterioles (Cech, 1973). Cat and sheep pulmonary arteries have even more dense cholinergic innervation, with AChE-positive nerve fibers displayed

down to vessels of 40 μm diameter (Hebb, 1969). Positively-stained nerve bundles and ganglionic cells have been found in the adventitia of the large rabbit and cat intrapulmonary veins (Hebb, 1969). Large intrapulmonary veins are also innervated with AChE-positive nerve fibers in sheep (Hebb, 1969). Although no AChE-positive nerve fibers have been found in human pulmonary arteries and veins (Partanen et al., 1982), cholinesterase staining has revealed cholinergic innervation of intrapulmonary arteries of the developing human fetus (Taylor and Smith, 1971; Pessacq, 1971). Both the density and extent of this innervation increase with age (Taylor and Smith, 1971).

Ultrastructural studies have confirmed the existence of cholinergic innervation to the pulmonary vascular tree in the dog and cat (Cech, 1973; Rhodin, 1978). In both species, bundles of nonmyelinated nerve fibers enclosed by Schwann cells were found in the adventitia of small arterioles down to 30 μm (Fillenz, 1970; Rhodin, 1978; Knight et al., 1981). Axons with vesicles are found within 150 nm of smooth muscle cells. Most varicosities are probably adrenergic, inasmuch as they contain small dense-cored vesicles (40 to 60 nm). Some of them (20 to 40%) are small agranular vesicles (40 to 60 nm), which is a characteristic morphological appearance of peripheral cholinergic nerve profiles (Fillenz, 1970; Rhodin, 1978; Kadowitz et al., 1976; Knight et al., 1981). Moreover, the histological appearance of this type of vesicle is not altered by 5- or 6-hydroxydopamine treatment (Kadowitz et al., 1976). Cholinergic vesicles have not been identified in the intrapulmonary veins of dogs (Fillenz, 1970).

2. Muscarinic receptors. Studies on the effects of ACh on the pulmonary circulation have proved to be contradictory, with both vasoconstrictor (Catravas et al., 1984; McLean, 1986; Sada et al., 1987) and vasodilator (Fritts et al., 1958; Nandiwada et al., 1983; Cherry and Gillis, 1987) responses being reported. Later, it was found that these conflicting results could be explained by the level of pre-existing tone. Thus, ACh induces a pressor response under resting conditions but causes a depressor response under conditions of elevated tone (Hyman and Kadowitz, 1988, 1989). There also seems to be a species variation in the ACh response, as both the mechanism and characteristics of the vasoconstrictor response in the rabbit are different from those in the cat pulmonary circulation (Catravas et al., 1984; Hyman and Kadowitz, 1988). In humans, ACh induces a clear vasodilator response, both under resting conditions and during acute hypoxic pulmonary vasoconstriction (Fritts et al., 1958).

Although ACh was the first identified endothelium-dependent vasorelaxant, binding studies have failed to identify the muscarinic receptor binding site on vascular endothelial cells in several arterial preparations (Stephenson and Summers, 1987; Summers et al., 1987), including the rabbit and rat pulmonary vasculature (Stephenson et al., 1988; De Michele et al., 1991). Thus, an alternative explanation has been proposed that ACh produces vasodilation via an intermediate step involving vascular smooth muscle (Summers et al., 1987). Using rabbit aortic endothelial cell membranes, Sim and Manjeet (1990) were able to demonstrate the presence of muscarinic receptors on endothelial cells. Evidence subsequently accumulated to indicate the existence of endothelial muscarinic receptors in the bovine aorta and coronary artery (Brunner and Kukovetz, 1991; Brunner et al., 1991). Muscarinic receptors are heterogeneous.

Five subtypes (M_1 to M_5) have been identified using molecular biological techniques, and M_1 to M_4 can be differentiated pharmacologically (Hulme et al., 1990). Muscarinic receptors mediating endothelium-dependent relaxations are classified as M_3-receptors in pulmonary arteries (McCormack et al., 1988). The muscarinic receptor subtypes on vascular smooth muscle seem to have a variable regional distribution (van Charldorp and van Zwieten, 1989; Mak and Barnes, 1990). Muscarinic receptors mediating the increase in pulmonary vascular resistance seem to be M_1-like receptors in rabbit (El-Kashef and Catravas, 1991), whereas both M_1- and M_2-receptors are involved in canine pulmonary vascular beds (El-Kashef et al., 1991). More recent results from autoradiographic mapping and in situ hybridization suggest that in human and guinea pig lung, M_3-receptors predominate, whereas in rabbit lung, M_4-receptors predominate in pulmonary vessels (Mak and Barnes, 1990, 1992, 1993). There are also M_1- and M_2-receptors on sympathetic and parasympathetic nerve endings, respectively (Maclagan et al., 1989), modulating norepinephrine and ACh release.

3. Cholinergic control of pulmonary vascular tone. Although the pulmonary circulation of many species is innervated with cholinergic nerves, their functional significance is less clear. These nerves do not seem to be important in the maintenance of low pulmonary vascular tone, inasmuch as cholinergic blockade does not alter basal PPA or vascular resistance (Murray et al., 1986). Earlier studies on the effects of vagal stimulation on the pulmonary circulation provided conflicting results. In the perfused lungs of the dog and guinea pig (Daly and Hebb, 1966), vagal stimulation induces pulmonary vasoconstriction. By contrast, pulmonary vasodilation is induced by vagal stimulation in adult pig (Mclean, 1986) and fetal lamb lungs (Rudolph, 1979). In the perfused pulmonary vascular bed of dog, Daly and Hebb (1952) showed that stimulation of the cervical vagosympathetic nerve trunk causes increased, decreased, or biphasic changes in PPA. This result is not surprising, because vagal nerves in the dog contain sympathetic nerve fibers (Daly and Hebb, 1952). Vagal stimulation is therefore likely to cause an adrenergic vasoconstriction as well as vasodilation. Furthermore, changes in cardiac output, airway pressure, and bronchial blood flow that are induced by vagal stimulation may also affect PPA. For example, vagal stimulation-induced increases in airway pressure would increase pulmonary vascular resistance

and therefore confound the decrease in PPA induced by vagal stimulation (Colebatch and Halmagyi, 1963). In the perfused cat lung, vagal stimulation evokes an increase in pulmonary perfusion pressure under basal conditions, whereas under conditions of elevated vascular tone, perfusion pressure decreases (Nandiwada et al., 1983). The pressor and depressor responses are blocked by phenoxybenzamine and atropine, respectively, confirming that both adrenergic vasoconstriction and cholinergic vasodilation are induced by vagal nerve stimulation. After chemical sympathectomy with 6-hydroxydopamine, vagal stimulation induced a frequency-dependent decrease in the lobar artery pressure under elevated vascular tone induced by both the thromboxane analog U44169 and hypoxia. Exogenously administered ACh mimics the response to vagal stimulation. The responses to both vagal stimulation and ACh are blocked by atropine and enhanced by physostigmine, a cholinesterase inhibitor. Moreover, this vagally induced vasodilation is not affected by elevating airway pressure or by reducing systemic blood pressure. Vagally released ACh acts on the vascular endothelium to induce NO release, which then causes vasodilation (McMahon et al., 1992). Human pulmonary arteries relax in response to ACh, and this response is lost when the endothelium is removed. Under these conditions, ACh induces a small contractile response (Greenberg et al., 1987a).

C. Nonadrenergic, Noncholinergic Mechanisms

1. Nonadrenergic, noncholinergic nerves. In addition to the classic adrenergic and cholinergic innervation, there are neural mechanisms that are not inhibited by adrenergic and cholinergic blockade (Barnes et al., 1991). NANC nerves may not represent separate neural pathways but are more likely to be manifestations of neurotransmission in sympathetic, parasympathetic, and sensory nerves. NANC neural responses that are excitatory (excitatory-NANC, vasoconstrictor) and i-NANC (vasodilator) have been demonstrated in pulmonary vessels electrophysiologically in rat small pulmonary arteries (Inoue and Kannan, 1988) and by EFS of precontracted pulmonary artery rings of guinea pig or cat (Kubota et al., 1988; Maggi et al., 1990; Liu et al., 1992a). In precontracted pulmonary artery rings, EFS induces a frequency-dependent relaxation, which is abolished by tetrodotoxin but is largely unaffected by treatment with a combination of adrenergic and cholinergic antagonists, indicating that the main component of this relaxation is mediated via NANC nerves (Maggi et al., 1990, Liu et al., 1992a). EFS also relaxes precontracted pulmonary arteries of dog, rabbit, and cow. However, these responses are not of neural origin, inasmuch as they are tetrodotoxin-resistant (Frank and Bevan, 1983, Greenberg et al., 1986; Buga and Ignarro, 1992).

2. Nonadrenergic, noncholinergic neurotransmitters. The neurotransmitters of NANC nerves in pulmonary vessels depend on the species used and on the size of vessel. ATP may act as an excitatory-NANC transmitter in pulmonary artery. In rat small intrapulmonary arteries, EFS evokes an excitatory junction potential that is (*a*) insensitive to adrenergic, cholinergic, histaminergic, and serotonergic blockade, (*b*) unaffected by catecholamine depletion or sympathetic denervation, but (*c*) is abolished by tetrodotoxin and inhibited by α,β-methylene ATP (Inoue and Kannan, 1988).

NO is the most likely i-NANC neurotransmitter in most organs studied (Rand, 1992), but neuropeptides such as VIP, SP, and CGRP may also be involved in neural vasodilator responses. CGRP-like immunoreactive nerves are located around pulmonary arteries of several species. (Lauweryns and Ranst, 1987; Mulderry et al., 1985). CGRP is likely to mediate the i-NANC response in large pulmonary arteries of guinea pig. CGRP-like immunoreactive substance is released upon electrical stimulation of these vessels (Maggi et al., 1990). CGRP mimics the NANC vasodilator response (Liu et al., 1992a), and CGRP receptors are localized to these vessels (Mak and Barnes, 1988). Moreover, pretreatment with capsaicin to deplete sensory neuropeptides markedly inhibits the i-NANC response (Liu et al., 1992a). An SP-like immunoreactive substance is also released during electrical stimulation in this vessel. However, SP is unlikely to be the i-NANC transmitter in this vessel, inasmuch as SP is an endothelium-dependent relaxant, whereas the i-NANC response is endothelium-independent in this vessel (Maggi et al., 1990; Liu et al., 1992a).

CGRP may not mediate the i-NANC response in the branch pulmonary arteries of guinea pig, however. CGRP does not mimic the i-NANC relaxation and has only a minimal relaxant effect in branch pulmonary arteries. The i-NANC response in the branch pulmonary arteries is partially endothelium-dependent, but CGRP is an endothelium-independent vasodilator in this vessel. Moreover, capsaicin treatments in vivo and in vitro have no significant effect on the i-NANC response in branch pulmonary arteries (Liu et al., 1992a). The i-NANC response is significantly inhibited by the P_{2y}-receptor antagonist, reactive blue 2, suggesting that ATP at least partially mediates the i-NANC response in guinea pig branch arteries (Liu et al., 1992a). NO also mediates the i-NANC response in these vessels.

3. Nitric oxide as i-nonadrenergic noncholinergic neurotransmitter. There is convincing evidence of NO action as an i-NANC neurotransmitter in pulmonary arteries (Liu et al., 1992b). In the presence of adrenergic and cholinergic blockade, EFS induces a transient, frequency-dependent relaxation of precontracted, endothelium-denuded, guinea pig pulmonary artery rings, which is abolished by tetrodotoxin. This i-NANC relaxation is markedly inhibited by the NO synthase inhibitors, L-NMMA or L-NAME, in a L-arginine reversible manner, with D-arginine being inactive (Liu et al., 1992b). Pyrogallol, an agent known to inactivate NO through super-

oxide radical generation, also inhibits the i-NANC relaxation, and the i-NANC relaxation is fully restored by adding superoxide dismutase at the peak of pyrogallol-evoked inhibition.

Inhibition of the formation of cGMP, the second-messenger of NO action, by methylene blue (5 μM) causes > 80% inhibition of the i-NANC relaxation. Additionally, the i-NANC relaxation is significantly potentiated by zaprinast, a type V PDE inhibitor that prevents cGMP degradation. Furthermore, i-NANC relaxation is accompanied by a marked increase in the tissue concentration of cGMP. The EFS-induced elevation in tissue cGMP concentration is significantly inhibited by L-NMMA. As discussed above, in endothelium-denuded pulmonary arteries, an NO synthase inhibitor significantly augments adrenergic contraction, without any effect on basal vascular tone or contraction evoked by exogenous norepinephrine, suggesting that there is neural release of NO, which acts as a functional antagonist to the adrenergic neural contractile response elicited by EFS (Liu et al., 1992b). However, it is unlikely that NO mediating the i-NANC vasodilator response to EFS is derived from adrenergic nerves, inasmuch as chemical sympathectomy with 6-hydroxydopamine has no effect on the NANC vasodilator response to EFS (Liu et al., 1992b). The possibility that NO is released from parasympathetic nerves as a cotransmitter with ACh is a possibility that cannot be further investigated until it is possible to selectively destroy these nerves. However, it is possible that NO may also be released by separate NANC nerves.

Although a large body of evidence supports the notion that NO mediates the NANC relaxant response, its source remains uncertain. The neuronal form of NO synthase has been localized to nerves innervating smooth muscle of pulmonary vessels (Klimaschewski et al., 1992), suggesting that NO is released from these nerve endings. Another possibility is that nerve stimulation induces transmitter release, which in turn causes NO release from smooth muscle or/and endothelial cells. NO derived from endothelial cells partially mediates the NANC vasodilator response in guinea pig pulmonary arteries, in contrast to bovine mesenteric and monkey cerebral arteries, where endothelially derived NO plays no role in mediating the NANC vasodilator response (Toda and Okamura, 1990; Ahlner et al., 1991). It is also possible that vascular smooth muscle may release NO when stimulated by transmitter released from NANC nerves, although there is little evidence to support the contention. The time course of NO production from these cells, which depends on inducible NO synthase, is too slow to account for neurotransmission.

4. Nonadrenergic, noncholinergic control of pulmonary vascular tone. Although i-NANC vasodilator, nerve-mediated pulmonary vasodilation has been demonstrated in vitro (Kubota et al., 1988; Maggi et al., 1990; Liu et al., 1992a), it has not been described in vivo. Therefore, the roles of this neural mechanism in the control of pulmonary vascular tone remain to be explored. Because the major part of the relaxant response to EFS is mediated through the i-NANC pathway, this neural mechanism may play a role in the regulation of pulmonary vascular tone and pulmonary blood flow. ATP modulates hypoxic pulmonary vasoconstriction (Benumof et al., 1982). Circumstantial evidence suggests that vagal sensory nerves and sensory neuropeptides have a protective action against fibrin-induced neurogenic pulmonary edema (Hashiba et al., 1989).

D. Reflex mechanisms

The pulmonary circulation is also under central and local reflex controls. Stimulation of the hypothalamic integrative area for the defense reaction causes a small increase in pulmonary vascular resistance (Anderson and Brown, 1967) or a decrease in pulmonary vascular compliance (Szidon and Fishman, 1981). Electrical stimulation of the medulla near the vascular regulatory C-1 area, in most experiments, induces sympathetically mediated pulmonary vasoconstriction, followed by a vasodilator response (Hyman, 1986). Stimulation of a discrete area in the forebrain also causes an abrupt pulmonary vasoconstriction followed by a prolonged pulmonary vasodilation. Both the constrictor and dilator responses are blocked by freezing or severing the spinal cord, indicating a pathway from forebrain through the spinal cord that regulates pulmonary vascular tone (Hyman, 1986). Elevation of intracranial pressure produces a pulmonary vasoconstriction via the Cushing reflex (Hessler and Cassin, 1977; Maron and Dawson, 1979). Intracranial hypertension-induced pulmonary vasoconstriction is likely to be the result of increasing circulating catecholamines released from the adrenal medulla (Maron and Dawson, 1979).

Pulmonary vascular tone is also modulated by peripheral chemoreceptors and baroreceptors. Depending on the experimental conditions, the stimuli, and the preexisting tone, stimulation of chemoreceptors in the carotid or aortic bodies increases PVR (Aviado et al., 1957; Daly and Daly, 1959; Daly and Hebb, 1966), decreases PVR (Daly and Daly, 1957; Fitzgerald et al., 1992), causes no change in PVR (Olson et al., 1982), or decreases pulmonary vascular compliance (Szidon and Flint, 1977). The increase in PVR and decrease in pulmonary vascular compliance are mediated by efferent sympathetic nerves (Daly and Hebb, 1966; Szidon and Flint, 1977), whereas the decrease in PVR is likely to be mediated via parasympathetic nerves (Daly and Daly, 1957; Olson et al., 1982; Wilson and Levitzky, 1989). Stimulation of baroreceptors in the carotid sinus or aortic arch by an elevation in blood pressure by reflex induces pulmonary vasodilation via a decrease in sympathetic outflow or activation of sympathetic vasodilator nerves (Daly and Hebb, 1966). It has been reported that bilateral carotid occlusion has little modulatory effect on pulmonary vascular resistance in anesthetized dogs, al-

though this does not exclude reflex modulation of pulmonary vasomotor activity (Pace, 1978).

Additionally, stimulation of receptors within the lungs can elicit a pulmonary reflex. Distension of the main pulmonary artery produces vasoconstriction (Hyman, 1968; Laks et al., 1975). This mechanism probably mediates the pulmonary vasoconstriction observed after pulmonary embolism (Stein and Levy, 1974). In contrast, stimulation of receptors in small pulmonary vessels by small emboli induces pulmonary vasodilation (Kealey and Brody, 1977).

Airway dynamics also affect pulmonary hemodynamics, via either central and/or local reflex pathways. One example is the decrease in the pulmonary arterial compliance after lung inflation (Ingram, 1972).

E. Possible Role in Pulmonary Vascular Disease

The role of pulmonary innervation in the HPV has been intensively studied. There are two components to the pulmonary vasoconstrictor response to hypoxia in intact animals, a local pulmonary vasoconstrictor response, and a reflex response. Although pulmonary innervation does not seem to play a role in the powerful local pulmonary vasoconstrictor response to acute hypoxia (Fishman, 1976; McLean, 1986), adrenergic nerves are likely to mediate the reflex increase in pulmonary vascular resistance or the decrease in pulmonary vascular compliance resulting from systemic hypoxemic stimulation of carotid and aortic chemoreceptors (Daly and Hebb, 1966; Szidon and Flint, 1977; McLean, 1986). Stimulation of carotid chemoreceptors during a local hypoxic pulmonary vasoconstrictor response blunts the HPV response. This attenuation of HPV has been suggested to be mediated via cholinergic nerves (Olson et al., 1982; Wilson and Levitzky, 1989), although inconsistent results have been reported (Lejeune et al., 1989).

It has been suggested that adrenergic nerves may protect against the development of pulmonary hypertension (McLean, 1986). However, there is no good evidence to support it. Adrenergic nerves are likely to mediate the pulmonary vasoconstriction seen in cold exposure (McLean, 1986), reperfusion (hypoperfusion followed by hyperperfusion) (Clougherty et al., 1988), pulmonary embolism (Price, 1955; Kabins et al., 1962), and neurogenic pulmonary edema (Colice et al., 1984; Malik, 1985). Adrenergic nerves are also involved in the development of embolic and neurogenic pulmonary edema (Kabins et al., 1962; Colice et al., 1984). Vagal nerves may also play a role in neurogenic pulmonary edema (Colice et al., 1984; Malik, 1985). Stimulation of both sympathetic and vagal nerves can increase lung weight gain or pulmonary vascular permeability to albumin (Sakakibara et al., 1992; Liu et al., 1994a).

Abnormalities in NANC vasodilator nerves may also contribute to the development of pulmonary hypertension. A decrease in CGRP-containing NANC vasodilator nerves has contributed to the development and maintenance of hypertension in spontaneous hypertensive rats (Kawasaki et al., 1990). Hypoxia inhibits NANC neuroeffector transmission in some nonvascular tissues (Bowman and McGrath, 1985). It is possible that the normal vasodilator action of NANC nerves is inhibited during hypoxia and may be impaired with repeated hypoxic episodes. Because NANC vasodilator nerves represent the major neural vasodilator mechanism of pulmonary vessels, abnormality in the NANC system could shift the balance toward vasoconstriction and potentiate the contractile response to vasoconstrictors such as hypoxia, thus potentiating HPV.

III. Humoral Mechanisms

Many circulating mediators and hormones have an effect on pulmonary vascular tone that is mediated via multiple receptors (table 2). The effects of these mediators and hormones on pulmonary vascular tone vary with species, age, and pre-existing tone. In general, A-II, NPY, leucine-enkephalin, thrombin, thrombin receptor activation peptide, PGs D_2, E_2 and $F_{2\alpha}$ are pulmonary vasoconstrictors, whereas ANP, VIP, CGRP, AMP, PGs E_1 and I_2 are pulmonary vasodilators. There are some exceptions; for example, PGD_2 and PGE_2 cause pulmonary relaxation in fetal lambs, and PGI_2 increases pulmonary vascular resistance in rabbits (see III.A.13. Eicosanoids). BK, AVP, endothelins, PACAP, SP, N-formyl-methionyl-leucyl-phenylalanine, histamine, 5-HT, PAF, arachidonic acid, adenosine, ADP and ATP have dual effects on pulmonary vascular tone, causing contraction when the vascular tone is low but relaxation when the vascular tone is high.

A. Effects of Humoral Substances on Pulmonary Vessels

1. Angiotensin II. A-II constricts isolated large pulmonary artery rings (Boe and Simonsson, 1981; Chand and Altura, 1981) and the perfused pulmonary vascular bed (Kadowitz et al., 1975; McMurtry, 1984; Goll et al., 1986;

TABLE 2
Humoral receptors in pulmonary vessels

Receptors	Subtypes	Responses	Endothelium-dependency
Adenosine	A_1	contraction	no
	A_2	relaxation	no
Angiotensin	AT	contraction	no
ANP	ANP_A	relaxation	no
	ANP_B	relaxation	no
Bradykinin	B_1?	relaxation	yes
	B_2	relaxation	yes
Endothelin	ET_A	contraction	no
	ET_B	relaxation	yes
Histamine	H_1	relaxation	yes
	H_2	relaxation	no
5-HT	5-HT_1	contraction	no
	5-HT_{1c}	relaxation	yes
Thromboxane	TP	contraction	no
Vasopressin	V_1	relaxation	yes

Liu et al., 1991b) via activation of its G-protein coupled receptors. Intravenous infusion of A-II substantially increases pulmonary arterial and venous pressure and decreases pulmonary blood flow volume, indicating vasoconstriction (Oakley et al., 1962). Endogenous A-II seems to be important in the regulation of pulmonary circulation (Goll et al., 1986). A-II has been proposed as a mediator of hypoxic pulmonary vasoconstriction (Berkov, 1974), but this was refuted (McMurtry, 1984). Endogenous production of A-II is likely to be reduced in hypoxia, inasmuch as hypoxia inhibits angiotensin-converting enzyme (Jin et al., 1987). Exogenous A-II has been reported to prevent hypoxic pulmonary hypertension and associated vascular changes and to inhibit acute HPV in the rat (Rabinovitch et al., 1988).

2. Kinins. BK and lysyl-BK (kallidin) are peptides synthesized de novo from high- and low-molecular-weight kininogen precursors that act via activation of B_2 (and under some circumstances B_1) receptors. BK is a potent NO releaser in both systemic and pulmonary vascular endothelial cells (Palmer et al., 1987; Ignarro et al., 1987b). Depending on the species, either only B_2 or both B_1 and B_2 kinin receptors are involved this response (Sung et al., 1988; Schini et al., 1990). BK also stimulates prostacyclin release from pulmonary vascular endothelium (Ignarro et al., 1987a). BK also stimulates afferent vagal C-fibers and thus may induce the release of sensory neuropeptides (Kaufman et al., 1980). Although BK dilates isolated pulmonary vascular rings, its effects on the intact pulmonary vascular bed depend on species and the preexisting vascular tone. Thus, BK either has no effect or constricts the pulmonary vascular beds of dog, sheep, rabbit, and rat under basal conditions (Hauge et al., 1966; Hauge, 1968; Levine et al., 1973; Pang et al., 1982) but induces vasodilation in fetal lamb (Frantz et al., 1989) or adult cat pulmonary vascular beds precontracted with a thromboxane analog (Lippton et al., 1984). Infusion of BK has no effects on the normal human pulmonary vascular bed but induces a moderate fall in PPA in patients with hypoxic pulmonary hypertension (Bishop et al., 1965). BK reverses hypoxic pulmonary vasoconstriction in human subjects in vivo and in isolated perfused rat lungs, presumably by release of NO (Segel et al., 1970; Archer et al., 1989).

3. Vasopressin. AVP is a circulating neurohormone and a potent systemic vasoconstrictor. Exogenous AVP is largely ineffective in isolated pulmonary artery rings (Chand and Altura, 1980; Ignarro et al., 1987a). Under resting conditions, AVP causes either vasoconstriction or a moderate vasodilator response in pulmonary vascular beds (Nyhan et al., 1986, 1987; Walker et al., 1989). AVP induces dilation of the pulmonary vascular bed precontracted with either vasoconstrictors or hypoxia (Walker et al., 1989; Russ and Walker, 1992). The vasodilator response to AVP seems to be mediated via V_1-receptors and NO release, because this response is blocked by a V_1-receptor antagonist and is markedly attenuated by an NO synthase inhibitor in an L-arginine reversible manner (Russ and Walker, 1992). Endogenous AVP is unlikely to be important in the regulation and/or modulation of pulmonary vascular tone (Walker et al., 1989), although it does delay onset of HPV (Jin et al., 1989). AVP suppresses DNA synthesis in cultured vascular smooth muscle (Murase et al., 1992). However, whether chronic treatment with AVP slows down the development of hypoxic pulmonary hypertension remains to be determined.

4. Atrial natriuretic peptides. The natriuretic peptide family consists of ANP, BNP, and CNP. Human ANP is a 28-amino-acid peptide that was originally thought to be synthesized in the atrium and later found to be synthesized in several other tissues (Gutkowska and Nemar, 1989). BNP is a 32-amino-acid peptide first isolated from porcine brain (Sudoh et al., 1988); its main source is ventricle (Nakao et al., 1992). CNP is a vascular natriuretic peptide produced from vascular endothelial cells. (Koller et al., 1991; Suga et al., 1992).

Natriuretic peptides exert their action via activation of specific receptors; these have been classified into three types according to their binding selectivity (Nakao et al., 1992). The rank order of ligand binding affinity for the ANP-A receptor is ANP $\geq$ BNP $\gg$ CNP; for the ANP-B receptor, CNP $>$ ANP $\geq$ BNP; and for the ANP-C receptor, ANP $>$ CNP $>$ BNP. Both ANP-A and ANP-B receptors are guanylyl cyclase-coupled receptors, whereas the ANP-C receptor is not and is thought to be a clearance receptor, which participates in the degradation of these natriuretic peptides (Nussenzveig et al., 1990). All three receptors and their mRNAs have been localized in the lung by binding and molecular biological techniques (Nakao et al., 1992). A detailed review on the ANP receptors and their signal transduction mechanisms was recently published (Anand-Srivastava and Trachte, 1993).

Pulmonary vessels exhibit a high density of ANP binding sites (Anand-Srivastava and Trachte, 1993). The most intensively studied natriuretic peptide is ANP, which has a wide range of biological effects including natriuresis, vasodilation, inhibition of renin secretion, and aldosterone secretion (Inagami, 1989). ANP relaxes isolated pulmonary vessel rings of several species, including human (Jansen et al., 1987; Lindberg and Andersson, 1988). ANP also causes pulmonary vasodilation in the perfused pulmonary vascular bed (Jin et al., 1988; Cigarini, 1989) and reduces pulmonary vascular pressure and resistance in patients with COPD (Adnot et al., 1989). ANP is an endothelium-independent vasodilator (Jansen et al., 1987), although it may interact with the endothelium. ANP inhibits endothelium-mediated vasorelaxation, presumably via a feedback mechanism caused by an increase of cGMP (Hogan et al., 1989). Conversely, NO-releasing agents inhibit endothelin-induced ANP release (Lew and Baertschi, 1992).

ANP modulates HPV and the development of hypoxic pulmonary hypertension (Adnot et al., 1988). Acute alveolar hypoxia causes the release of ANP (Baertschchi and Teague, 1989). Circulating ANP level is increased in animal models of chronic hypoxic pulmonary hypertension and in patients with pulmonary hypertension (McKenzie et al., 1986; Adnot et al., 1987; Winter et al., 1989). Chronic infusion of ANP reduces the thickness of small pulmonary vascular wall in rats exposed to hypoxia (Zhao et al., 1991). Elevation of endogenous ANP levels by inhibition of neutral endopeptidase cause a significant reduction in the hypoxia-induced pulmonary vascular remodelling and right ventricular hypertrophy (Stewart et al., 1992). Furthermore, treatment of rats with a monoclonal antibody to ANP before hypoxia exposure aggravates pulmonary hypertension and right ventricular hypertrophy (Raffestin et al., 1992). Transgenic mice that carry a fusion gene composed of the transthyretin promoter and the mouse ANP structural gene (transthyretin-ANP mice) have higher plasma ANP levels and lower pulmonary and right ventricular systolic pressures. These mice have less right ventricular hypertrophy and pulmonary arteriolar muscularization compared with nontransgenic control animals after exposure to hypoxia for 3 weeks (Klinger et al., 1993). ANP also inhibits the proliferation of cultured vascular smooth muscle cells (Abell et al., 1989; Itoh et al., 1990). These results suggest that ANP can participate in a negative feedback mechanism to slow down the development of hypoxic pulmonary hypertension.

ANP may be involved in other pulmonary vascular diseases. There is a good correlation during exercise between plasma ANP concentration and PPA in patients after coronary angioplasty (Scholz et al., 1990). High plasma ANP levels have also been observed in patients with high-altitude edema (Bartsch et al., 1988). In normal mountaineers exposed to hypoxia, ANP improves pulmonary gas exchange (Westendorp et al., 1993).

5. Endothelins. Endothelins are a family of 21-amino-acid isopeptides named ET-1, ET-2, and ET-3, which are encoded by three distinct ET genes (Inoue et al., 1989). The synthesis and vascular effects of these isopeptides have been reviewed elsewhere (Haynes and Webb, 1993). Endothelins have widespread effects on pulmonary function, including the pulmonary circulation (Barnes, 1994). Immunocytochemistry and molecular biology studies have demonstrated that ET-1 is the major isoform expressed and secreted in endothelial cells, although ET-2 immunoreactivity has been detected in endothelial cells (Howard et al., 1992; Haynes and Webb, 1993). ET-3 immunoreactivity or mRNA cannot be detected in endothelial cells (Bloch et al., 1989; Howard et al., 1992).

Endothelin effects are mediated through activation of specific receptors designated as ET_A- (ET-1 = ET-2 $\gg$ ET-3) and ET_B-receptors (ET-1 = ET-2 = ET-3), which have been cloned, and possibly also through ET_C-receptors (ET-3 > ET-1 = ET-2). Molecular biology and binding data indicate that ET-receptors on pulmonary vascular smooth muscle cells are of the ET_A type and on vascular endothelial cells are of the ET_B type (Hosoda et al., 1991; Ogawa et al., 1991). The exception is rabbit pulmonary artery, where ET_A- and ET_B-receptors apparently coexist on vascular smooth muscle (LaDouceur et al., 1993). Several ET_A-receptor agonists and antagonists have been developed (Haynes and Webb, 1993).

Depending on vasomotor tone, ET isopeptides can cause either pulmonary vasoconstriction or vasodilation. Under baseline conditions, ETs (ET-1 and ET-2) constrict pulmonary vascular rings of pig (Sudjarwo et al., 1993), sheep (Toga et al., 1992b), guinea pig (Hay et al., 1993), and human (McKay et al., 1991; Hay et al., 1993). In perfused pulmonary vascular beds under basal conditions, ETs (ET-1 and ET-3) increase PPA and/or pulmonary vascular resistance in several species (Toga et al., 1991; Mann et al., 1991; Horgan et al., 1991; Crawley et al., 1992a). ET-1 is more potent than ET-2 and ET-3 in the contractile response (McKay et al., 1991; Crawley et al., 1992a). When vascular tone is elevated either naturally (as in the fetus) (Perreault and de Marte, 1991; Wong et al., 1993) or artificially (Hasunuma et al., 1990; Toga et al., 1991; Lippton et al., 1991; Crawley et al., 1992a), these peptides induce a dose-related pulmonary vasodilation. Isolated pulmonary vascular rings from adult sheep seem to be more sensitive than those from fetal and neonatal sheep, and vein seems to be more sensitive than artery in the contractile response to ET-1 (Toga et al., 1992b). The contractile response is mediated by ET_A-receptors, and relaxation by ET_B-receptors (Hay et al., 1993; Sudjarwo et al., 1993). An atypical ET_B-receptor-mediated contraction has been reported in swine pulmonary veins (Sudjarwo et al., 1993). The signal transduction mechanism between receptor activation and contractile response to ETs remains to be elucidated but may involve mobilization of both extracellular and intracellular Ca, activation of protein kinase C (Mann et al., 1991), and inhibition of adenylate cyclase (Vogelsang et al., 1994). Cyclo-oxygenase products may also contribute to ET-1-induced contraction in pulmonary veins (Toga et al., 1991; Horgan et al., 1991). Activation of ATP-sensitive K^+ channels and release of NO are involved in mediating the relaxant response to ETs (Hasunuma et al., 1990; Lippton et al., 1991; Crawley et al., 1992a; Tod and Cassin, 1992).

Under in vivo conditions, ET may affect pulmonary vascular tone via other mechanisms. It has been reported that ET-1 enhances adrenergic contraction postjunctionally but inhibits norepinephrine release prejunctionally (Wiklund et al., 1989b). ET-1 stimulates the conversion of A-I to A-II, suggesting that ET-1 may influence pulmonary vascular tone through the generation of A-II (Kawaguchi et al., 1990).

The role of ETs in various pathophysiological conditions have been intensively studied. Both ET-1 and ET-3

reverse HPV (Crawley et al., 1992a; Hasunuma et al., 1990). Rats exposed to chronic hypoxia for 3 weeks show an impaired relaxant response to ET-1 (Eddahibi et al., 1991). However, ET-1 is unlikely to be an important modulator of HPV but rather a contributor to the development of pulmonary hypertension. Although hypoxia has been reported to either have no effect or to reduce ET-1 secretion from cultured porcine or bovine pulmonary vascular endothelial cells (Wiebke et al., 1992; Hassoun et al., 1992), human vascular endothelial cells cultured in hypoxic conditions secrete eight-fold more ET-1 compared with ambient oxygen conditions, and there is an increase in prepro-ET-1 mRNA expression within 1 h of hypoxia, which is reversible when returned to 21% O_2 (Kourembanas et al., 1991). Rats exposed to hypoxia for 2 days show a three-fold increase in plasma ET-1 levels and a two-fold increase in ET-1 mRNA expression in the lung and right atrium but not in the organs perfused by the systemic circulation (Elton et al., 1992). Increased ET-1 immunoreactivity in lung homogenates or endothelial cells and increased mRNA expression of prepro-ET-1 has also been observed in rat models of idiopathic pulmonary hypertension (Stelzner et al., 1992) and in patients with both hypoxic and other types of pulmonary hypertension (Stewart et al., 1991; Yoshibayashi et al., 1991; Giaid et al., 1993). ET-1 stimulates (*a*) DNA synthesis and cell proliferation of cultured pulmonary vascular smooth muscle cells (Janakidevi et al., 1992; Hassoun et al., 1992), and (*b*) the replication of pulmonary artery fibroplasts (Peacock et al., 1992). This response seems to be mediated via ET_A receptors, because the ET_A receptor antagonist, BQ-123, inhibits ET-1 mediated proliferation (Zamora, et al., 1993b). In rat models of monocrotaline-induced pulmonary hypertension, chronic infusion of BQ-123 inhibits the progression of pulmonary hypertension, arterial medial thickening, and right ventricular hypertrophy (Miyauchi et al., 1993). Plasma ET-1 concentration is elevated during and after pulmonary surgery (Onizuka et al., 1991) and in patients with ARDS (Druml et al., 1993; Langleben et al., 1993).

6. Vasoactive intestinal polypeptide. The VIP family comprises a group of structurally related peptides including VIP, peptide histidine isoleucine, peptide histidine methionine, peptide histidine valine, helodermin, PACAP, secretin, and growth hormone-releasing factor. VIP-immunoreactive nerve fibers are widely distributed in the lung (Barnes et al., 1991), and seem to innervate pulmonary vessels (Dey et al., 1981; Dey and Said, 1985; Barnes et al., 1986). VIP relaxes isolated pulmonary vessel rings (Hamasaki et al., 1983; Barnes et al., 1986; Greenberg et al., 1987b) and dilates the intact pulmonary vascular bed (Nandiwada et al., 1985; Minkes et al., 1992). VIP is 30 times more potent than ACh and 1000 times more potent than isoproterenol in isolated pulmonary artery rings (Hamasaki et al., 1983) but is less potent than cholinergic and β-adrenergic agonists in the intact pulmonary vascular bed (Nandiwada et al., 1985). VIP has been reported to be either an endothelium-dependent (Ignarro et al., 1987a) or an endothelium-independent (Barnes et al., 1986) vasodilator in bovine pulmonary arteries. The reason for this discrepancy is unclear. The NO synthase inhibitor, L-NAME, has no effect on the VIP-induced relaxation in cat pulmonary vascular bed (Minkes et al., 1992). Autoradiographic studies show a high density of VIP receptors in pulmonary vascular smooth muscle in guinea pigs and humans with no labelling of endothelial cells (Carstairs and Barnes, 1986a). Peptide histidine isoleucine is also a pulmonary vasodilator (Greenberg et al., 1987b). In the cat pulmonary vascular bed perfused at constant flow, PACAP produces a contraction when vascular tone is low and a dilation when vascular tone is elevated (Minkes et al., 1992). The contraction is mediated by endogenous catecholamine release. PACAP is three-fold more potent than VIP in relaxing the cat pulmonary vasculature. NO is involved in the PACAP-induced relaxation in systemic vessels (Gardiner et al., 1994). These mechanisms have not yet been reported in pulmonary vessels.

7. Calcitonin gene-related peptide. CGRP is a 37-amino-acid peptide. Two forms, α-CGRP and β-CGRP, have been described, and both are expressed in sensory neurons (Barnes et al., 1991). CGRP-immunoreactive nerves are abundant in the lung, frequently innervating pulmonary vessels (Mulderry et al., 1985; Lauweryns and Ranst, 1987). CGRP is costored and colocalized with tachykinins, with a distribution pattern consistent with that of sensory neurons (Lundberg et al., 1985; Martling, 1987) and is depleted by capsaicin treatment (Martling, 1987). CGRP is released during stimulation of the vagus nerve (Martling, 1987) and upon stimulation of the perivascular nerves of guinea pig main pulmonary arteries. CGRP may be a neurotransmitter of i-NANC vasodilator nerves of cat and guinea pig large pulmonary arteries (Maggi et al., 1990; Liu et al., 1992a), as discussed above in II.C.3.

CGRP is a potent vasodilator of guinea pig and human pulmonary arteries in vitro (McCormack et al., 1989d; Liu et al., 1992a). CGRP is more potent in relaxing large than in relaxing smaller pulmonary arteries of guinea pigs (Liu et al., 1992a). In the perfused cat pulmonary vascular bed at basal condition, CGRP has little effect on basal perfusion pressure but dose-dependently decreases perfusion pressure when the vascular tone is elevated artificially (Lippton et al., 1990). Activation of the adenylyl cyclase-linked CGRP receptors increases tissue cAMP content and results in vasodilation (Barnes et al., 1991). CGRP has been demonstrated to induce NO release and to increase tissue cGMP levels in rat aortic rings (Wang et al., 1991), and CGRP-induced systemic hypotension in conscious rat is partially abrogated by L-NAME (Abdelrahman et al., 1992), suggesting NO may play a role in the systemic vasodilator response to CGRP. Whether the same mechanism exists in pulmo-

nary circulation remains to be determined. Mechanical removal of endothelium has no effect on the vasodilator responses to CGRP in human pulmonary vessels in vitro, suggesting that CGRP acts directly on vascular smooth muscle cells (McCormack et al., 1989d). This is consistent with an autoradiographic study that demonstrated the CGRP receptors on vascular smooth muscle but not on endothelial cells in pulmonary arteries and veins of all dimensions (Mak and Barnes, 1988). Although depletion of sensory neuropeptides, including CGRP, by pretreatment of rats with capsaicin has little effect on the acute HPV response (McCormack et al., 1993), CGRP may counteract the development of hypoxic pulmonary hypertension. CGRP-like immunoreactivity is increased in lung neuroendocrine cells of rats exposed to chronic hypoxia (McBride et al., 1990; Roncalli et al., 1993). Chronic infusion of CGRP prevents, and immunoneutralization with CGRP antibody, or infusion of CGRP receptor antagonist peptides exacerbate, hypoxic pulmonary hypertension in rats exposed to chronic hypoxia (Tjen-A-Looi et al., 1992).

8. Substance P. SP belongs to the tachykinin family, which includes NK A (NKA), NK B (NKB), NP K (NPK), and NP-γ (Nakanishi, 1991). SP is predominantly synthesized in the nodose and jugular ganglia of the vagus nerve and transported down the vagus to the lungs. SP seems to be localized predominantly in the capsaicin-sensitive unmyelinated nerves in the lung. SP-like immunoreactive nerve fibers are distributed around pulmonary vessels in several species (Dey et al., 1981; Furness et al., 1982).

Tachykinin effects are mediated by specific receptors designed as NK_1, NK_2, and NK_3 receptors. NK_1 receptors are activated preferentially by SP, NK_2 receptors by NKA, and NK_3 receptors by NKB (Nakanishi, 1991). Tachykinin receptors on pulmonary vessels are NK_2 receptors on smooth muscle and NK_1 receptors on vascular endothelium (Carstairs and Barnes, 1986b; D'Orleans-Juste et al., 1986; McCormack et al., 1989e). NK_2 and NK_3 receptors are probably absent on pulmonary vascular endothelium, inasmuch as NKA and NKB have no effects on the precontracted endothelium-intact pulmonary arteries (Maggi et al., 1990). SP induces constriction of isolated pulmonary vascular rings at resting tension via stimulation of NK_2 receptors (Tanaka and Grunstein, 1985; D'Orleans-Juste et al., 1986) but causes relaxation of precontracted preparations through activation of endothelial NK_2 receptors (Tanaka and Grunstein, 1985; D'Orleans-Juste et al., 1986; Maggi et al., 1990; Liu et al., 1992a). In the intact pulmonary vascular beds perfused at constant flow and under basal conditions, SP has no effect in dogs (Archer et al., 1986a), increases PPA in guinea pigs and rabbits (Worthen et al., 1985; Selig et al., 1988), and slightly reduces PPA in cats (McMahon and Kadowitz, 1993). When pulmonary vascular tone is elevated by hypoxia or other vasoconstrictors, SP decreases pulmonary vascular pressure in all species studied (Archer et al., 1986a; Adnot et al., 1991a; McMahon and Kadowitz, 1993). The contractile response to SP is partially mediated by cyclooxygenase products (Worthen et al., 1985; Selig et al., 1988), whereas the endothelium-dependent relaxation is mainly mediated by NO release (Maggi et al., 1990; Liu et al., 1992a; McMahon and Kadowitz, 1993). Recently, SP has been reported to enhance TNF-α secretion in inflammatory cells (Luber-Narod et al., 1994), suggesting that SP may induce pulmonary vasodilation via an indirect mechanism under inflammary conditions.

9. Neuropeptide Y. NPY is a 36-amino-acid neuropeptide localized to adrenergic and other nerves. NPY-immunoreactive nerve fibers are present in the adventitia of pulmonary vessels (Sheppard et al., 1984). NPY has several actions in the lung (Barnes et al., 1991) and acts predominantly as a cotransmitter in adrenergic nerves. NPY is synergistic with adrenergic contraction (Lippton et al., 1990) and is a pulmonary vasoconstrictor in vitro (Obara et al., 1989). However, NPY has little effect on the pulmonary vascular bed, nor does it alter the pulmonary vasoconstrictor response to norepinephrine and other vasoconstrictors (Lippton et al., 1990). NPY stimulates prostacyclin production in cultured vascular endothelial cells (Kawamura et al., 1991).

10. Other Peptides. Bombesin is a weak pulmonary vasoconstrictor in vitro (Dey and Said, 1985), but neither bombesin nor its C-terminal analog, gastrin-releasing peptide, is vasoactive in intact pulmonary vascular beds (Mulik et al., 1983). Calcitonin is also inactive in the pulmonary vascular bed (Gillespie et al., 1984). Morphine increases PPA and pulmonary vascular resistance via activation of opioid receptors and indirectly by stimulating the release of histamine, which causes vasoconstriction through activation of H_1 receptors (Hakim et al., 1992). The endogenous opioid, leucine-enkephalin, is also a pulmonary vasoconstrictor (Gillespie et al., 1984). Cholecystokinin relaxes precontracted isolated pulmonary artery rings, whereas neurotensin is inactive (Obara et al., 1989), although both are constrictors of airway smooth muscle (Barnes et al., 1991). The bacterial chemoattractant peptide, N-formyl-methionyl-leucyl-phenylalanine, causes either contraction or relaxation of isolated pulmonary vascular rings (Crowell et al., 1989; Laplante et al., 1989) but induces constriction in the perfused pulmonary vascular bed (Tanaka et al., 1992). Somatostatin has no effect on either isolated pulmonary vascular rings (Obara et al., 1989) or on the perfused pulmonary vascular bed under basal conditions but preserves hypoxic pulmonary constriction, which decays with time (Sakai and Voelkel, 1988). In isolated pulmonary artery rings, thrombin causes a transient relaxation followed by a sustained contraction. Removal of endothelium or an NO synthase inhibitor abolishes or inhibits the relaxant component and augments the contractile component, suggesting that NO plays a role in mediating the transient relaxation response to thrombin

(Glusa et al., 1994). Thrombin and thrombin receptor activation peptide (a proteolytic thrombin receptor cleaved by thrombin) increases the perfusion pressure in the guinea pig but decreases the perfusion pressure in neonatal piglet pulmonary vascular beds (Lum et al., 1994; Pinheiro et al., 1993). The increased pulmonary perfusion pressure seems to be caused mainly by pulmonary venoconstriction (Lum et al., 1994), whereas the decreased pulmonary perfusion pressure is primarily induced through arteriolar dilation (Pinheiro et al., 1993). Both extracellular Ca^{2+} entry and phosphoinositide hydrolysis are involved in the pulmonary vasoconstrictor response to thrombin or thrombin receptor activation peptide (Glusa et al., 1994; Lum et al., 1994).

11. Histamine. Histamine is released from mast cells in the lung. These cells are localized to the adventitia of pulmonary vessels. Histamine causes either constriction or dilation of the isolated pulmonary vascular rings and perfused pulmonary vascular bed depending on existing tone, inducing constriction when the vessels are at resting tension (Okpaka, 1972) but eliciting dilation when the tone is elevated by norepinephrine (Abcioglu et al., 1987) or hypoxia (Silove and Simcha, 1973). The contractile response is mediated by H_1-receptors on vascular smooth muscle cells, and the relaxant response is mediated by both H_2-receptors on smooth muscle and H_1-receptors located on vascular endothelial cells (Abcioglu et al., 1987; Matsuki and Ohhashi, 1990; Szarek et al., 1992). NO seems to be responsible for the endothelium-dependent relaxation in pulmonary arteries of rats (Szarek et al., 1992), but both PGI_2 and NO are involved in the relaxation of human pulmonary arteries (Ortiz et al., 1992). Histamine also constricts pulmonary veins by activation of H_1-receptors (Barman and Taylor, 1989). In the intact lung, histamine has both precapillary and postcapillary actions, with the latter dominant (Shirai et al., 1987). There seem to be developmental changes in the pulmonary vascular response to histamine in the sheep (Gordon et al., 1991).

Histamine evokes oscillatory membrane potassium and chloride currents through the release of intracellular Ca^{2+} from caffeine-sensitive Ca^{2+} stores (Wang and Large, 1993), and this may be the mechanism of its vasoconstrictor action.

12. 5-Hydroxytryptamine. 5-HT or serotonin is produced by activated platelets and has been suggested as a mediator of pulmonary hypertension in the presence of pulmonary thromboemboli (Comroe et al., 1953). Indeed, 5-HT is a potent pulmonary vasoconstrictor in several species (Hyman et al., 1982; McMurtry, 1986), causing vasoconstriction even under conditions of elevated tone (Hyman et al., 1982). However, 5-HT relaxes pulmonary vessels in other species when vascular tone is high. Thus, 5-HT relaxes precontracted pulmonary vascular beds of cats (Neely et al., 1993), and induces endothelium-dependent relaxation of isolated pulmonary arteries of pigs (Glusa and Richter, 1993) and pulmonary veins of sheep (Cocks and Arnold, 1992). 5-HT contracts human pulmonary arteries and veins in vitro (Raffestin et al., 1985) yet has no effect on PPA in vivo (Harris et al., 1960). This may be caused by the balancing between its vasoconstrictor and vasodilator effects. Both $5\text{-}HT_1$ (MacIntyre et al., 1993) and $5\text{-}HT_2$-receptors (Raffestin et al., 1985; Le Roux and Syce, 1989; McMahon et al., 1993b) are involved in the contractile response to 5-HT, whereas the relaxant response to 5-HT is mediated via $5\text{-}HT_1$ receptors (Neely et al., 1993; Glusa and Richter, 1993). 5-HT stimulates the endothelial $5\text{-}HT_{1C}$ receptors and triggers the release of NO, leading to pulmonary vasodilation (Cocks and Arnold, 1992; Glusa and Richter, 1993). 5-HT stimulates and inhibits bovine pulmonary vascular smooth muscle proliferation in vitro (Lee et al., 1991a). Tyrosine phosphorylation and elevation of *c-myc* and actin mRNA seem to be prerequisites for the stimulation of DNA synthesis (Lee et al., 1994), whereas activation of $5\text{-}HT_{1A}$ receptors and elevation of cAMP mediate the inhibitory effect of 5-HT on smooth muscle proliferation (Lee et al., 1991a). 5-HT released from platelets contributes to the initiation and progression of monocrotaline-induced pulmonary hypertension (Kanai et al., 1993).

13. Eicosanoids. Arachidonic acid is an essential fatty acid and an integral component of different phospholipid pools in the cell membranes. Activation of phospholipase by a variety of stimuli via either Ca^{2+}-dependent or Ca^{2+}-independent pathways induces the release of arachidonic acid and lyso-PAF, the latter being the precursor of PAF. Upon release, arachidonic acid may be metabolized via two main pathways: the 5′-lipoxygenase pathway leading to the production of LTs and the cyclooxygenase pathway leading to the formation of PGs and Tx A_2 (TxA_2).

Arachidonic acid itself constricts the perfused pulmonary vascular bed when the vascular tone is low (Wicks et al., 1976; Selig et al., 1986) but relaxes the vascular bed when the vascular tone is elevated by hypoxia (Gerber et al., 1980). The contractile responses to arachidonic acid are caused in large part by the formations of TxA_2 and other prostanoids (Selig et al., 1986; McMahon et al., 1991b). The endoperoxide intermediate, PGH_2, is also a pulmonary vasoconstrictor in the adult (Kadowitz et al., 1977; Gruetter et al., 1978), but in fetal lambs, a pulmonary vasodilator response has been reported (Tod et al., 1986). The primary prostaglandins formed from this intermediate include PGD_2, PGE_2, $PGF_{2\alpha}$, and PGI_2. Although pulmonary vasodilator responses to PGD_2 (Ford et al., 1990; Perreault et al., 1990) or PGE_2 (Lock et al., 1980; Cassin et al., 1981a) have been reported in fetal and early neonatal lambs, PGD_2, PGE_2 and $PGF_{2\alpha}$ usually act as pulmonary vasoconstrictors (Kadowitz, 1975), with $PGF_{2\alpha}$ being the most potent (Kadowitz, 1975; Hyman et al., 1982). In contrast, PGI_2 is usually a vasodilator (Hyman and Kadowitz, 1979), although PGI_2 has been reported to increase vascular

resistance in the blood-perfused rabbit pulmonary vascular bed, via stimulation of TxA_2 synthesis (Kaapa et al., 1991). PGE_1 relaxes pulmonary vessels at elevated tone (Hyman and Kadowitz, 1979). TxA_2 and its stable breakdown product TxB_2 are pulmonary vasoconstrictors (Friedman et al., 1979; Kadowitz and Hyman, 1980). Some of the vasoconstrictor effect of TxA_2 seems to be mediated by the induction of LTC_4 and LTD_4 formation (Soifer et al., 1989). TxA_2 is reported to mediate the endothelium-dependent contractile response to arachidonic acid and methacholine in rabbit pulmonary artery in vitro (Buzzard et al., 1993).

The lipoxygenase metabolites of arachidonic acid, LTA_4, LTB_4, LTC_4, and LTD_4, have diverse biological activities, including effects on pulmonary vessels. LTB_4, C_4, and D_4 cause contraction of isolated pulmonary vessel rings of guinea pig (Hand et al., 1981), pig (Ohtaka et al., 1987; Paterson et al., 1988), and human (Hanna et al., 1981), and the intact pulmonary vascular bed in vivo (Ahmed et al., 1985; Noonan and Malik, 1986) or in situ (Voelkel et al., 1984; Albert et al., 1989). The effects of LTs are mediated by specific LT-receptors (Voelkel et al., 1984) and also via the release of cyclo-oxygenase products (Ahmed et al., 1985). Both endothelium-dependent contractile and relaxant responses to LTC_4 and LTD_4 have been reported in systemic vessels (McLeod and Piper, 1992; Pawloski and Chapnick, 1993). Whether the same mechanism exists in pulmonary vessels remains to be determined.

Recently, a noncyclo-oxygenase, free radical-catalyzing effect of arachidonic acid has been described. Metabolism of arachidonic acid through this pathway leads to the production of $PGF_{2\alpha}$-like compounds in humans in vivo (Kang et al., 1993). One of the compounds formed by this pathway is 8-epiprostaglandin $F_{2\alpha}$, which causes pulmonary vasoconstriction via the generation of TxA_2 (Kang, et al., 1993). This compound constricts both pulmonary arteries and veins with a potency twice as great as $PGF_{2\alpha}$.

The role of these arachidonic acid metabolites in HPV and various pulmonary vascular pathological conditions, especially in hypoxic or other types of pulmonary hypertension, has been the subject of intensive investigation. However, their definitive roles under these conditions are still unclear. Some of the metabolites may contribute to development of pulmonary vascular disease, such as pulmonary hypertension, in some animal models but have no clear role in other animals. The complex interaction between these mediators, either synergistic or antagonistic, makes it very difficult to evaluate their role. Cyclo-oxygenase products (especially TxB_2) and lipoxygenase (LTB_4) seem to contribute to the early pulmonary hypertension seen in sepsis or TNF_α-induced lung injury (Wheeler et al., 1992; Kuratomi et al., 1993). TxB_2 may also contribute to the pulmonary hypertension seen in ischemia-reperfusion lung injury (Zamora et al., 1993a). Patients with pulmonary hypertension secondary to congenital heart disease have significantly higher plasma TxA_2 and lower PGI_2 levels compared with normal subjects, suggesting an imbalance between constrictor and dilator cyclo-oxygenase products. Interestingly, plasma TxA_2 levels return to normal 1 year after corrective surgery (Adatia et al., 1993a). Cyclo-oxygenase products may participate in the regulation of pulmonary vascular tone during cardiopulmonary preservation (Mashburn et al., 1989).

14. Platelet-activating factor. PAF is a lipid mediator derived from lyso-PAF, which is released from membrane phospholipids by the same conditions that release arachidonic acid and acts on specific surface PAF-receptors. PAF has potent cardiovascular effects that vary according to species, age, physiological conditions, and concentration (McMurtry, 1986; vandongen, 1991). In adult animals under resting conditions, PAF causes systemic hypotension, pulmonary hypertension, and pulmonary edema (Voelkel et al., 1982; Burhop et al., 1986; Bellan, et al., 1992; Shibamoto et al., 1993). By contrast, PAF constricts both systemic and pulmonary vessels, with significant venoconstriction occurring in the fetal lamb (Toga et al., 1992a). PAF induces pulmonary vasoconstriction when the vascular tone is low (Voelkel et al., 1982; Burhop et al., 1986; Pritze et al., 1991) but causes vasodilation when the vascular tone is high (McMurtry and Morris, 1986; Chen et al., 1992). Leukotrienes and TxA_2 play an important role in mediating the vasoconstrictor response to PAF in dog (Yamanaka et al., 1992), rat (Davidson and Drafta, 1992), and lamb (Toga et al., 1992a), but have no role in the PAF-induced vasoconstriction in the cat (Bellan et al., 1992).

Prostaglandins may contribute to the pulmonary vasodilator response to PAF (Yamanaka et al., 1992). NO may also be involved in this response, inasmuch as the pulmonary vasorelaxant response to PAF in vitro is endothelium-dependent (McMurtry and Morris, 1986). PAF is able to trigger NO release in systemic vessels or vascular beds (Moritoki et al., 1992; Bellan et al., 1992). Although PAF reverses HPV (McMurtry and Morris, 1986; Chen et al., 1992), it is unlikely to be involved, because PAF antagonists do not modify the response (Haynes et al., 1988; McCormack et al., 1989a). PAF may contribute to the development of chronic hypoxic pulmonary hypertension, however. Chronic infusion of PAF into rabbits over a 4-week period results in both hemodynamic and morphological changes similar to those seen in pulmonary hypertension (Ohar et al., 1990; Ohar et al., 1991). PAF is released into lavage fluids in rats exposed to hypoxia (Prevost et al., 1984). Newborn humans with persistent pulmonary hypertension have high plasma PAF levels (Caplan et al., 1990). Chronic PAF treatment enhances pulmonary arterial reactivity to some vasoconstrictors in isolated pulmonary vascular beds (Ohar et al., 1993). Moreover, treatment of rats with a specific PAF receptor antagonist slows down the

development of hypoxic pulmonary hypertension (Ono et al., 1992).

15. Purines. Purine nucleosides and nucleotides include adenosine, AMP, ADP, and ATP. These purine compounds have long been known to be vasoactive and have been implicated in many physiological and pathophysiological processes (Olsson and Pearson, 1990; Daval et al., 1991). Purine receptors can be subdivided into P_1- and P_2-purinoceptors, which are selective for adenosine and ATP, respectively (Burnstock and Kennedy, 1985). P_1-receptors (adenosine receptors) can be further subclassified into A_1, A_2 (A_{2A} and A_{2B}) and A_3 receptors (Collis and Hourani, 1993). These subtypes of adenosine receptor belong to the G-protein coupled receptor superfamily and are encoded by different genes (Collis and Hourani, 1993). Likewise, P_2-receptors can also be further divided into P_{2x} and P_{2y} subtypes (Burnstock and Kennedy, 1985; Olsson and Pearson 1990). Other subtypes have been proposed but need to be confirmed (Olsson and Pearson, 1990). P_1-receptors on pulmonary vessels have been characterized as A_1 and A_2 subtypes (McCormack et al., 1989c) and P_2-receptors as P_{2x} and P_{2y} subtypes (Liu et al., 1989a, b). P_{2x} receptors are located on smooth muscle, whereas P_{2y} receptors are located on endothelium of rat pulmonary vessels, but on the vascular smooth muscle of human small pulmonary arteries (Liu et al., 1989a, b). It is not clear whether this is a regional or a species-dependent variation.

Both adenosine and ATP have dual effects on isolated pulmonary vessels, causing concentration-dependent contraction in vessels at resting tension and inducing relaxation of precontracted vessel rings (McCormack et al., 1989c; Wiklund et al., 1989a; Liu et al., 1989a, b). The contraction is mediated via A_1 or P_{2x} receptors located on smooth muscle, whereas relaxation is mediated by A_2 or P_{2y} receptors (McCormack et al., 1989c; Liu et al., 1989a, b). Adenosine increases PPA and pulmonary vascular resistance in adult sheep and cat pulmonary vascular beds (Biaggioni et al., 1989; Lippton et al., 1992) but decreases PPA and vascular resistance in fetal and newborn lambs (Konduri et al., 1992a, b). Adenosine is a pulmonary vasodilator, both in normal volunteers (Reid et al., 1990) and in patients with various types of pulmonary hypertension (Morgan et al., 1991b; Haywood et al., 1992). Similarly, ATP constricts adult cat pulmonary vascular beds (Lippton et al., 1992) but relaxes the pulmonary vascular beds of fetal sheep (Konduri et al., 1992a). ATP reduces pulmonary vascular resistance in patients with COPD with and without pulmonary hypertension (Gaba et al., 1986). These results suggest that there are both vascular tone- and species-dependent variation in response to purines.

Purines may regulate pulmonary vascular tone via neuronal pathways. ATP is coreleased from sympathetic nerve endings with norepinephrine (von Kugelgen and Starke, 1991) but inhibits norepinephrine release prejunctionally from these nerves (McLean, 1986) via activation of P_{2y} purinoceptors (Allgaier et al., 1994). Adenosine, ADP, and AMP are also coreleased with norepinephrine upon electrical field stimulation of intramural nerves in rabbit pulmonary arteries (Mohri et al., 1993). ATP may act as neurotransmitter or mediator of pulmonary NANC vasodilator nerves (Liu et al., 1992a). Adenosine also modulates adrenergic neuroeffector transmission (Wiklund et al., 1989a) and has been reported to inhibit vagal motor neurone excitability via activation of A_1 receptors (Markes et al., 1993). Shear stress caused by flow evokes ATP release, which in turn causes NO release and pulmonary vasodilation (Hassessian et al., 1993). Under in vivo conditions, this could be another mechanism for the ATP-mediated regulation of pulmonary vascular tone.

Cyclo-oxygenase products (probably TxA_2) are involved in the adenosine-induced pulmonary vasoconstriction (Biaggioni et al., 1989; Lippton et al., 1992). Inhibition of adenylyl cyclase and lowering of cellular cAMP levels are another mechanism for the A_1 receptor-mediated contraction (Olsson and Pearson, 1990; Daval et al., 1991). Mechanisms contributing to the A_2-mediated relaxation include activation of adenylyl cyclase (Olsson and Pearson, 1990; Daval et al., 1991), inhibition of Ca^{2+} influx, and modulation of inositol phospholipid turnover (Zhou et al., 1992). An important mechanism for ATP-induced vasorelaxation is stimulation of NO release (Liu et al., 1989a, 1992a). Adenosine and ATP may also participate the O_2-induced pulmonary vasodilation that occurs at birth (Konduri et al., 1993). Both adenosine and ATP have been reported to have mitogenic effects on cultured human endothelial and vascular smooth muscle cells (Ethier et al., 1993; Erling et al., 1993).

16. Cytokines. Cytokines are a group of small protein mediators with diverse biological actions, including mediation or modulation of inflammation, cell growth and differentiation, immunity and tissue repair. Cytokines themselves are not vasoactive, but they can influence vascular tone via stimulation or inhibition of vasoactive mediators. One example of this is the cytokine or endotoxin induction of an iNOS, leading to the formation of large amounts of NO, which is believed to be an important contributor to hypotension in septic shock (Kilbourn et al., 1990; Stoclet et al., 1993). The iNOS gene is not transcribed under normal conditions but is switched on during inflammation and after stimulation with inflammatory mediators or bacterial endotoxin. Several cytokines, including interleukin-1β, TNF-α, and interferon-γ, have been shown to induce the iNOS gene expression in cultured pulmonary vascular smooth muscle cells (Nakayama et al., 1992). Treatment with bacterial endotoxin in vivo also induces the expression of iNOS gene in the lung (Liu et al., 1993), heart, aorta, and pulmonary arteries (Liu et al., 1994b). Induction of iNOS and formation of NO also accounts for the pulmo-

nary vascular hyporeactivity seen in endotoxemia (Griffiths et al., 1993).

Cytokines also affect the constitutive eNOS. After a single dose of TNF-α in vivo, rats show an impaired dilator response to ACh and an enhanced HPV response (Liu et al., 1992c), whereas the relaxant response to nitroprusside is similar to that in saline-treated control lungs (Liu et al., 1992c). Similar results have been reported in pulmonary vascular beds of rats and guinea pigs treated with TNF-α in vivo (Stevens et al., 1992; Johnson and Ferro, 1992). Treatment of isolated bovine pulmonary artery rings with TNF-α in vitro causes a concentration-dependent inhibition of the relaxant response to ACh and BK associated with a reduction of NO release as detected by both bioassay and chemiluminescence NO (Xie et al., 1993). Moreover, TNF-α down-regulates eNOS mRNA in cultured human umbilical vein endothelial cells (Yoshizumi et al., 1993). Thus, cytokines inhibit eNOS and induce iNOS gene expression.

The effects of cytokines on pulmonary vascular reactivity or vascular tone may depend on the balance of the opposing effects of cytokines on eNOS and iNOS. It is of interest that treatment of rats with identical doses of TNF-α for 20 min, but not for 3 min or 24 h, enhances the pulmonary pressor response to hypoxia and A-II (Stevens et al., 1992). Likewise, chronic treatment of rats with TNF-α for 1 week increases—whereas for 2 weeks decreases—pulmonary vascular reactivity (Stevens et al., 1992, 1993), suggesting that the effects of TNF-α on iNOS and eNOS may be dose- and/or time-dependent. More studies are needed to determine whether these changes are similar to the pulmonary hemodynamic changes seen in septic shock.

There may be a species-dependent variation in the response to TNF-α. In isolated perfused canine lobes, TNF-α treatment for 30 minutes abolishes the HPV response (Johnson et al., 1993). However, the loss of HPV may not be related to the induction of iNOS, inasmuch as the NO synthase inhibitor L-NMMA has no effect on the loss of HPV response induced by TNF-α (Johnson et al., 1993). This is consistent with the lack of basal NO activity in dog pulmonary vessels (Nishiwaki et al., 1992; Barnard et al., 1993).

Like NOS, cyclo-oxygenase also has its constitutive (COX-1) and inducible (COX-2) isoforms. Cytokines, LPS and other inflammatory mediators induce the expression of COX-2 mRNA and protein in a dexamethasone-inhibitable manner (Fu et al., 1990; Hla and Neilson, 1992). This provides molecular and biochemical evidence of the involvement of cyclo-oxygenase products in the pulmonary vasomotor changes during endoxemia (Hales et al., 1981). Thus, cytokines can affect pulmonary vascular tone through the alterations of NOS or COX activities, or both.

B. Humoral Control of Pulmonary Vascular Tone

Although the pulmonary vasculature responds actively to many humoral and autacoid factors, as discussed in III.A., their precise physiological roles and involvement in disease states have not yet been elucidated. Inhibition of the production of these substances, or blockade of their receptors, have no effect on basal pulmonary vascular tone, suggesting that none of these substance is primarily responsible for the maintenance of the normal low pulmonary vascular tone (McMurtry, 1986). However, these results do not necessarily exclude the possibility that these substances contribute to the low pulmonary vascular tone to some extent. Inasmuch as the pulmonary vascular bed is under the influence of a large number of vasoconstrictor and vasodilator substances, it is possible that eliminating the effects of one or two mediators may not result in a clear-cut change in pulmonary vascular tone, because such a change could well be compensated by increased activity of other mediators.

The maintenance of low pulmonary vascular tone seems to be the result of a balance between these vasoconstrictors and vasodilators (Robin, 1982), with the latter holding sway under normal physiological conditions. Other factors such as recruitment of vessels, distensibility of the pulmonary vasculature, the meagerness of smooth muscle, low basal α-adrenergic activities (Vogal and Blount, 1965), and the ability of pulmonary endothelial cells to take up and/or remove many systemically or locally released vasoconstrictor substances may also contribute to the low pulmonary vascular tone. As detailed above, autacoid and inflammatory mediators exert many effects on the pulmonary circulation. A-II, ANP, AVP, ATP, ACh, BK, dopamine, ET-1, ET-3, PAF, PGD_2, PGI_2, and SP have been reported to inhibit acute pulmonary vasoconstriction elicited by hypoxia, suggesting that these substances may modulate HPV. Cyclooxygenase and 5′-lipoxygenase may be involved in HPV (see Physiological adaptation, next section).

1. Physiological adaptation. The pulmonary circulation undergoes significant changes during physiological adaptations to exercise, pregnancy, cold exposure and perinatal pulmonary vascular adaptation. Humoral mechanisms may play an important role in these physiological adaptation responses. The pulmonary circulatory response to exercise is an increase in blood flow caused by increased cardiac output, an increase in P_{PA}, and a slight decrease in PVR. Both passive factors and active vasodilation contribute to the decrease in PVR (Reeves et al., 1989). Vasodilator prostaglandins may be contributory but are unlikely to be important in the exercise-induced pulmonary vasodilation (Reeves et al., 1989). An increase in blood flow during exercise stimulates NO release, which may be responsible for the pulmonary vasodilation during exercise (Kane et al., 1994).

The pulmonary circulation during pregnancy is in a dilated state with low P_{PA} and PVR, despite blood volume expansion and an increase in cardiac output. Although no mediator has been identified to account for this, the decreased PVR is likely to be induced by a general reduction in pulmonary vasoreactivity to vasoconstrictors, thus shifting the balance toward vasodilation (Moore, 1989). Vasodilators may also increase during pregnancy. One of many humoral changes during pregnancy is an increase in circulating estrone/estradiol, which are pulmonary vasodilators (Moore, 1989). Estrogen receptors are located on vascular endothelial cells (Moore, 1989). Estradiol or estrogen has been shown to enhance the constitutive nitric oxide synthase gene expression and constitutive nitric oxide synthase activity (Schray-Utz et al., 1993; Lizasoain et al., 1993). An increased NO synthesis has been reported in pregnant rats (Conrad et al., 1993). Thus, an increase in NO release during pregnancy can contribute to the low P_{PA} and low PVR.

The pulmonary circulatory responses to short-term cold exposure are increases in cardiac output and P_{PA} and pulmonary vasoconstriction, resulting in an increase in PVR (McMurtry, 1986). HPV and increased α-adrenoceptor stimulation by neurally and humorally released norepinephrine account for the increase in PVR (McMurtry, 1986).

2. Changes at birth. There seem to be multiple mechanisms mediating the transition of the fetal pulmonary circulation to that of the adult, with a complex interaction between anatomical, mechanical, physical, and humoral factors. Changing from fluid-filled to gas-filled lungs by ventilation results in the formation of an air-liquid interface, which tends to reduce perivascular pressure (Cassin et al., 1964). Hypoxia is an important mechanism underlying the high pressure and high resistance of fetal pulmonary circulation (Rudolph and Yuan, 1966). A high PCO_2 content also contributes to the high pulmonary blood pressure (Rudolph and Yuan, 1966). Increases in inspiratory O_2 and decreases in blood PCO_2 could exert vasodilator effects (Morin et al., 1988). Mediators such as BK (Melmon et al., 1968) and A-II (Davidson, 1987) may also play a role. Endothelium-derived PGI_2 and NO play an important role (see V.H.).

C. Possible Role in Pulmonary Vascular Disease

Although most of the humoral substances discussed have impressive actions on pulmonary vascular tone and other cellular functions, their pathophysiological roles in pulmonary vascular diseases largely remain unclear. This is mainly caused by a lack of specific inhibitors or receptor antagonists that are effective in vivo.

1. Role in hypoxic pulmonary hypertension. The roles of humoral substances in the development of chronic HPH have been intensively studied. There are two components to the HPH: pulmonary vasoconstriction and vascular remodelling, characterized by medial thickening of small pulmonary arteries and right ventricular hypertrophy. Although there exists no conclusive evidence of a role of any single humoral mediator in the development of HPH, several humoral mediators may contribute the process of HPH through the mediation of pulmonary vasoconstriction or stimulation of pulmonary vascular smooth muscle proliferation, or both. Substances contributing to HPH include ET-1 (Miyauchi et al., 1993), PAF (Ono et al., 1992), arachidonic acid metabolites, 5-HT, and histamine (McMurtry, 1986). In contrast, ANP, AVP, and CGRP inhibit the development of HPH, either via pulmonary vasodilation, or by inhibiting vascular smooth muscle proliferation, or both. Angiotensin-converting enzyme inhibitors have been reported to inhibit the development of HPH (Kentera et al., 1981). However, the enzyme activity is likely to be reduced under conditions of chronic hypoxia (Jin et al., 1987). Several conventionally used vasodilators inhibit the development of HPH, presumably through a nonspecific pulmonary vasodilator action (McMurtry, 1986).

2. Pulmonary hypertension. Humoral mediators may also play a role in the development of other types of pulmonary hypertension. 5-HT has been implicated in the pathogenesis of pulmonary hypertension due to familial platelet storage pool disease (Herve et al., 1990). TxA_2, ET-1, and 5-HT are reported to contribute to the development of monocrotaline-induced pulmonary hypertension (Miyauchi et al., 1993; Kanai et al., 1993). ET-1 may also play a role in rat model of idiopathic pulmonary hypertension (Stelzner et al., 1992). Because PGI_2 plays an important role in the perinatal pulmonary vasodilation, loss of this mechanism due to endothelial damage may contribute to newborn persistent pulmonary hypertension (Stenmark et al., 1989). Likewise, endothelium-derived NO may also play a part in the perinatal pulmonary vasodilation (Abman et al., 1990); loss of NO might contribute to this condition.

3. Pulmonary embolism. Two major pathophysiological changes seen in pulmonary embolism are pulmonary hypertension and pulmonary vascular injury. Although mechanical obstruction of the pulmonary vascular bed is an important factor resulting in pulmonary hypertension, humoral factors released from leukocytes, platelets, mast cells, macrophages, and pulmonary endothelial cells contribute to the development of both pulmonary hypertension (Malik, 1983) and lung injury (Malik and Johnson, 1989). Clot embolism in dogs leads to release of 5-HT, and 5-HT receptor antagonists reduce pulmonary hypertension during embolism (Utsunomiya et al., 1981). Similarly, glass bead or clot embolism in dogs, rabbits, and sheep induce the release of histamine (Tucker et al., 1976b) and TxB_2 (Utsunomiya et al., 1982; Garcia-Szabo et al., 1983). The increase in pulmonary vascular resistance is reduced by histamine antagonists (Tucker et al., 1976b) and inhibition of TxA_2 synthesis (Utsunomiya et al., 1982). The role of 5-HT in pulmonary embolism has been questioned, inasmuch as

the normal human pulmonary vascular bed seems to be unresponsive to this agent in vivo (Harris and Heath, 1986). However, 5-HT constricts human pulmonary arteries in vitro (Raffestin et al., 1985). Moreover, pulmonary vascular reactivity may alter under pathological conditions. For example, endogenous 5-HT increases P_{PA} in patients with PPH (Herve et al., 1990). Vasodilators with diverse mechanisms of action reduce pulmonary vascular resistance in patients with pulmonary hypertension secondary to recurrent pulmonary embolism, suggesting that in addition to pulmonary vascular obstruction, there is a vasoconstrictor component (Dantzker and Bower, 1981). Additionally, activated neutrophil- or macrophage-derived inflammatory mediators such as PAF, LTB_4, TNF-α, interleukin-1β, and reactive oxygen species may be important in the pulmonary vascular injury after pulmonary embolism (Malik and Johnson, 1989).

4. Adult respiratory distress syndrome. Pulmonary hypertension associated with an increase in pulmonary vascular resistance is frequently observed in animal models and patients with ARDS (Rounds, 1989). The abnormal pulmonary circulatory control can influence both the extent of pulmonary edema and the systemic hypoxemia that characterize ARDS. Two main mechanisms responsible for pulmonary hypertension in ARDS are pulmonary vasoconstriction and vascular obstruction. Humoral mediators are important in the pulmonary hypertension seen ARDS. Cyclo-oxygenase products, particularly TxA_2, are likely to be the mediators of pulmonary hypertension in endotoxin, PAF, thrombin, and clot-induced lung injury, but not in oleic acid-induced lung injury (Rounds, 1989). Lipoxygenase products of arachidonic acid may also play an important role in the pulmonary hypertension seen with endoxemia (Ahmed et al., 1986; Rounds, 1989). There is evidence to indicate that 5-HT may mediate the pulmonary hypertension after autologous clot infusion (Hechtman et al., 1984; Rounds, 1989). Another important factor contributing to the pulmonary hypertension seen in lung injury, particularly that induced by endotoxin, is down-regulation of the eNOS (Yoshizumi et al., 1993). Loss of endothelium-derived NO will predispose vascular smooth muscle to vasoconstriction and enhance pulmonary vasoconstrictor responses (Liu et al., 1992c; Stenens et al., 1992). Lung injury involves complex endothelial and inflammatory cell interactions (Rounds, 1989), and multiple inflammatory mediators and cytokines are undoubtedly involved.

5. Pulmonary edema. Substances such as BK (Pang et al., 1982), ET-1 (Rodman et al., 1992; Simmet et al., 1992), histamine (Raud et al., 1991; Yuan et al., 1993c), 5-HT (Sumita et al., 1989; Raud et al., 1991), LTB_4 (Raud et al., 1991), PAF (Chan et al., 1994) and SP (Brain and Williams, 1985) are edema-forming or promoting agents and may therefore participate in the formation of inflammatory and other types of pulmonary edema. By contrast, CGRP (Raud et al., 1991) and VIP (Said, 1990) have anti-inflammatory properties and therefore may be protective against the development of pulmonary edema. Adenosine has also been reported to contribute to the platelet-mediated reduction of endothelial albumin permeability (Paty et al., 1992).

IV. Respiratory Gases

Pulmonary vascular tone is under the active influence of respiratory gases. Both hypoxia and hypercapnia induce pulmonary vasoconstriction (Fishman, 1961), but increases in mixed venous CO_2 is the main stimulus for the hypercapnic response, whereas decreased mixed venous PO_2 is only a contributory factor in the hypoxic response (Duke, 1954; Marshall and Marshall, 1983). The principal stimulus for HPV is alveolar hypoxia (Duke, 1954; Marshall and Marshall, 1983).

A. Hypoxic Pulmonary Vasoconstriction

HPV is a physiological response whereby circulating blood is diverted away from hypoxic alveoli, thus optimizing the matching of perfusion and ventilation and maximizing arterial oxygenation. Because it is unique and perhaps the most powerful active control mechanism in the pulmonary circulation, HPV has been an area of intensive investigation and much debate since it was first described by Von Euler and Liljestrand (1947). Von Euler and Liljestrand initially suggested that HPV resulted from the constriction of small muscular pulmonary arteries (several hundred μm in diameter) in response to alveolar hypoxia. This was confirmed by Kato and Staub (1966). Subsequently, Glazier and Murray (1971) found, using rapid freezing techniques, that hypoxia primarily constricted small pulmonary arteries. This site was further confirmed by pulmonary arteriograms (Shirai et al., 1986) and by the demonstration of hypoxic constriction primarily in pulmonary arteries (30 to 200 μm) in bullfrog lungs (Koyama and Horimoto, 1983). Direct micropuncture measurements of intrapulmonary vascular pressure further supported this conclusion by showing that the predominant site of HPV is the precapillary arteries (Nagasaka et al., 1984). On the other hand, measurements by means of dimension transducers and functional approaches have also demonstrated venoconstriction in response to hypoxia (Morgan et al., 1968; Dawson et al., 1979). Nevertheless, most investigators have concluded that the small pulmonary arteries are the major site of HPV.

1. Mechanisms. Despite more than four decades of investigation, the mechanism of HPV remains unclear (Voelkel, 1986). Early work established that autonomic innervation does not seem to be necessary for the pressor response of the adult lung to hypoxia (Fishman, 1976; Szidon and Flint, 1977; Hales and Westphal, 1979), based on several lines of evidence. Firstly, HPV persists in isolated lung preparations (Hauge, 1968;

Hauge and Melmon, 1968) and in human transplanted lungs (Robin et al., 1987). Secondly, HPV is unaffected by adrenoceptor blockade (Malik and Kidd, 1973), catecholamine depletion (Goldering et al., 1962; Silove and Grover, 1968), sympathectomy (Fishman, 1961), or depletion of sensory neuropeptides with capsaicin (McCormack et al., 1993). Thus, intrinsic mechanisms within the lung seem to be responsible for HPV. Two main hypotheses have been proposed. One is the mediator hypothesis, in which endogenous vasoconstrictors or vasodilators are believed to be released or suppressed by hypoxia, thus initiating HPV. The other hypothesis proposes a direct effect of hypoxia on the pulmonary vascular smooth muscle, inducing contraction (fig. 2).

In the search for chemical mediators, many vasoactive substances have been considered as candidates, including catecholamines (Fishman, 1976), histamine (Hauge, 1968; Hauge and Melmon, 1968), A-II (Berkov, 1974), vasoconstrictor prostaglandins (Weir et al., 1976), 5-HT (Fishman, 1976), PAF (McCormack et al., 1989a), ATP (McCormack et al., 1989b), and others. As discussed in III.A., none of these has proved to be essential for HPV, although these substances may have a modulatory role or might play a role in setting up the background conditions that are necessary for HPV to occur. LTC_4 and LTD_4 are still under consideration (Morganroth et al., 1984; Lonigro et al., 1988; McDonnell et al., 1990; Richalet et al., 1991), but their definitive role in HPV still remains to be confirmed. ET-1 may play a role in the development of chronic hypoxic pulmonary hypertension but is unlikely to mediate acute HPV, as the onset of the contractile response and recovery after washout are much slower than the time course of HPV.

The idea that suppression of vasodilator production, such as BK, by hypoxia could mediate HPV was first proposed by Weir (1978). Although BK has been eliminated as a candidate, many other endogenous vasodilators, such as NO and PGI_2, remain possible. This aspect will be discussed later, in the next section.

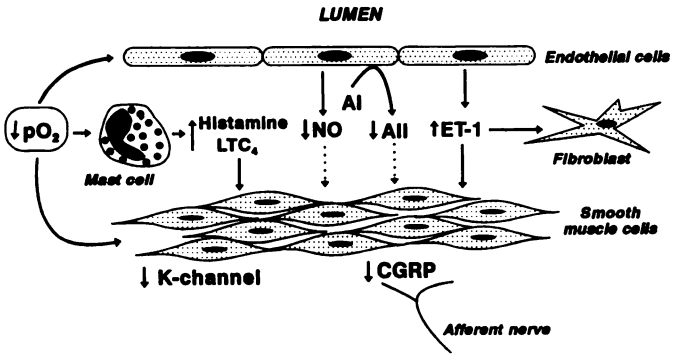

FIG. 2. Mechanisms of hypoxic pulmonary vasoconstriction. Pulmonary vascular tone may increase with hypoxia because of reduced release of relaxants from endothelial cells, via release of mediators from other cells, or by a direct effect of hypoxia on the smooth muscle cell.

Failure to identify conclusive mediator(s) has promoted the alternative proposal that HPV is caused by a direct effect on pulmonary vascular smooth muscle cells. In support of this hypothesis, small pulmonary arteries of cat (Madden et al., 1985) and human (Hoshino et al., 1988) contract in response to hypoxia in vitro, and hypoxia contracts pulmonary vascular smooth muscle cells in culture (Murray et al., 1990). Several possible mechanisms have been proposed to explain how hypoxia directly causes pulmonary vasoconstriction. Hypoxia closes a K^+ channel and causes membrane depolarization of the carotid body type I cells (Lopez-Lopez et al., 1989), which has led to the suggestion that hypoxia may close oxygen-sensitive K^+ channels, which leads to smooth muscle depolarization and Ca^{2+} entry, thus inducing contraction. Several K^+ channels have been described in pulmonary vascular smooth muscle cells (see VI.E.). Hypoxia inhibits both voltage-gated and Ca^{2+}-activated K^+ channels, and induces depolarization of pulmonary artery smooth muscle cells, but not renal or mesenteric artery smooth muscle cells (Post et al., 1992; Yuan et al., 1993b; Cornfield et al., 1994). Additional evidence supporting this suggestion is the the demonstration that hypoxia causes Ca^{2+} influx into cultured pulmonary artery smooth muscle cells of adult rats (Salvaterra and Goldman, 1993) and fetal lambs (Cornfield et al., 1994). However, ATP-dependent K^+ channels have been shown to mediate secondary vasodilation rather than the initial constriction to severe hypoxia (Wiener et al., 1991). The energy state hypothesis suggests that HPV is initiated by decreased oxidative phosphorylation (Rounds and McMurtry, 1981; Stanbrook and McMurtry, 1983). The cytochrome P_{450} hypothesis proposes that cytochrome P_{450} acts a sensor that initiates HPV (Miller and Hales, 1979). The redox hypothesis states that oxygen tension regulates the production of reactive oxygen species or peroxide, which control transmembrane Ca^{2+} flux and hence vascular tone through a direct action on sulfhydryl groups in the Ca^{2+}-channel protein of vascular smooth muscle (Archer et al., 1986b, 1993). All these hypotheses are still being explored, but any hypothesis needs to account for the difference in response to hypoxia of vascular smooth muscle in the pulmonary and systemic circulations.

2. Abnormalities in pulmonary vascular disease. Alterations in the HPV response may occur in several clinical conditions. HPV is lost or greatly diminished in various types of lung injuries. Loss or diminished HPV response has been observed in lungs treated with hyperoxia (Newman et al., 1981), hydrogen peroxide (Burghuber et al., 1984), endotoxin (Reeves et al., 1974; Hales et al., 1981), and bleomycin (McCormack et al., 1992). Either blunted (Leeman et al., 1992) or unchanged (Johnston et al., 1989) HPV responses have also been reported in the oleic acid-induced lung injuries of dogs. In contrast, lung injury induced by α-napthylthyiourea or monocrotaline potentiates HPV responses (Hill and

Rounds, 1983; Gillespie et al., 1986). Lungs treated with TNF-α also show an increased HPV response without obvious lung injury (Liu et al., 1992c). The differing vascular reactivities in these lung injury models may relate to differences in the extent or site of injury or may reflect different stages of lung injury. The alterations in pulmonary vascular reactivity during lung injury induced by endotoxin, α-napthylthyiourea, or monocrotaline is not specific to hypoxia, inasmuch as the reactivity to other pharmacological stimuli is also altered (Hales et al., 1981; Hill and Rounds, 1983; Gillespie et al., 1986). On the other hand, bleomycin-induced lung injury diminishes the HPV response, without affecting the constrictor response to A-II (McCormack et al., 1992). The HPV response is absent or diminished in an animal model of *Pseudomonas aeruginosa* pneumonia (Hanly et al., 1987), in atelectasis (Thomas and Garrett, 1982), and in some, but not all, patients with hepatic cirrhosis (Daoud et al., 1972; Rodriguez-Roisin et al., 1987). This could at least partially account for the severe hypoxemia seen in these conditions. Elevations in pulmonary and left atrial pressure blunt HPV, which may partially explain the abnormal ventilation/perfusion matching and hypoxemia associated with severe congestive or mitral heart disease and volume overload (Benumoff and Wahrenbrock, 1975). There are also reports that the HPV response is blunted in some patients with chronic bronchitis (Weitzenblum et al., 1988), asthma (Corte and Young, 1985), and suspected pulmonary embolism (Sostman et al., 1983). The mechanism and significance of the altered HPV response in these clinical conditions are not clear.

The effects of chronic hypoxia on the HPV response are somewhat conflicting. In rats exposed to chronic hypoxia, some investigators reported a decreased response (McMurtry et al., 1980; Hill and Ou, 1984), whereas others demonstrated an increased pressor response (Emery et al., 1981; Park et al., 1977). Variations in age or strain of animals and the duration of hypoxic exposure may explain these contradictory results. It has recently been reported that rats exposed to hypoxia for 15 h or 2 days exhibit a markedly reduced HPV response, whereas rats exposed to hypoxia for 7 days show an HPV response similar to that in control rats (Zhao et al., 1993). The decreased or increased HPV response after chronic hypoxia is associated with a decreased or increased pressor response to other pharmacological stimuli, suggesting an alteration in pulmonary vascular reactivity. An enhanced HPV response has been observed during lung hyperinflation (Quebbeman and Dawson, 1977) in dogs with hypothermia (Fan et al., 1992) and in patients with systemic hypertension (Guazzi et al., 1989). The clinical significance of the increased HPV response is unclear. The HPV response can be inhibited by multiple vasodilator mediators or drugs (see section III.). This emphasizes the importance of assessing gas exchange as well as hemodynamics when using these agents.

The mechanisms responsible for the alteration in HPV response in disease are largely unknown. Endothelial damage may account for the hyperreactivity seen after α-napthylthyiourea- or monocrotaline-induced lung injury (Hill and Rounds, 1983; Gillespie et al., 1986). Production of vasodilator prostaglandins may contribute to the pulmonary vascular hyporeactivity seen in endoxemia (Hales et al., 1981). It is now clear that induction of an inducible NO synthase and increased formation of NO are largely responsible for endotoxin-induced pulmonary vascular hyporeactivity (Liu et al., 1993).

V. Role of Endothelium

A. Endothelium-Derived Relaxing Factor

In 1980, Furchgott and Zawadzki demonstrated that the vascular relaxation induced by ACh was dependent on the presence of an intact vascular endothelium. They also demonstrated that ACh-induced smooth muscle relaxation resulted from the endothelium-mediated release of a nonprostanoid, labile relaxing substance later termed EDRF (Cherry et al., 1982). The phenomenon of endothelium-dependent relaxation was subsequently observed in a wide range of vascular preparations including arteries, veins, and microvessels of various regions in response to a diverse range of pharmacological and physiological stimuli (Furchgott, 1984; Furchgott and Vanhoutte, 1989). Furchgott (1988) and Ignarro (Ignarro et al., 1988b) independently suggested that EDRF may be NO, based on the pharmacological similarities between EDRF and NO generated from either acidified NO_2^- or NO gas, and evidence now strongly supports the identification of EDRF as NO (Moncada et al., 1991; Nathan, 1992). Another proposed nonprostanoid EDRF that differs from NO is EDHF (Komori and Vanhoutte, 1990). In the physiological salt solution perfused pulmonary vascular bed of rat, ACh-induced vasodilation is not inhibited by NO synthase inhibitors such as L-NMMA, although BK-induced relaxation is inhibited (Archer et al., 1989). ACh-induced vasodilation is consistently inhibited by NO synthase inhibitors in the pulmonary vascular beds of cat and lamb (Fineman et al., 1991a; McMahon et al., 1991a). Differences in agonist efficacy in the receptor system being studied might explain the agonist- and tissue-dependent variation in the L-NMMA effect (Martin et al., 1992). Whether EDRF, in addition to NO and EDHF, exists remains to be determined.

1. Role of basally released nitric oxide. The importance of NO in the regulation of pulmonary vascular tone is evident by the demonstration that many humoral factors and autacoids induce pulmonary vasodilation through the release of NO. Substances that have been reported to induce pulmonary vasodilation through endothelium-derived NO release include ACh (McMahon

et al., 1991a, 1992), norepinephrine (Liu et al., 1991a), BK (Ignarro et al., 1987a), SP (Maggi et al., 1990; McMahon and Kadowitz, 1993), ATP (Liu et al., 1992a), histamine (Szarek et al., 1992; Ortiz et al., 1992), 5-HT (Glusa and Richter, 1993), ET-1 and ET-3 (Crawley et al., 1992a).

Acute infusion of L-NMMA or oral administration of L-NAME for periods of 4 weeks causes a dose-dependent increase in systemic arterial blood pressure that is associated with a reduction in aortic cGMP content (Rees et al., 1989; Arnal et al., 1992), indicating that basally released NO plays an important role in the regulation of systemic blood pressure. The role of basal levels of NO released into the pulmonary circulation seems to be variable between species. L-NMMA or L-NA increase baseline PPA in pulmonary vascular beds of guinea pigs (Davidson and Eldemerdash, 1991), rabbits (Wiklund et al., 1990), and lambs (Fineman et al., 1991a; Gordon and Tod, 1993). L-NA reduces pulmonary vascular conductance with no change in PPA in the pigs in vivo, suggesting an increase in pulmonary vascular resistance during L-NA infusion (van Gelderen et al., 1993). Methylene blue also increases PPA in the pulmonary vascular beds of cats (Hyman et al., 1989). By contrast, L-NA or L-NAME have no effect on pulmonary vascular resistance in dogs, either under basal conditions or when the pulmonary venous pressure is slightly elevated to ensure that the circulation is under zone 3 conditions (Nishiwaki et al., 1992; Barnard et al., 1993). L-NMMA or hemoglobin increase baseline vascular tone in isolated pulmonary artery rings of pigs and guinea pigs (Liu et al., 1992a, d) or lambs (Abman et al., 1991) but not rats (Crawley et al., 1990). L-NMMA or L-NA have no effects or slightly increase pulmonary perfusion pressure in the perfused pulmonary vascular bed under basal conditions (Archer et al., 1989; Hasunuma et al., 1991a; Liu et al., 1991b) but increase PPA or vascular resistance in hypertensive pulmonary vascular beds (Oka et al., 1993; Barer et al., 1993) or when the venous pressure is slightly elevated to ensure that the pulmonary vascular beds are under zone 3 conditions in the rats (Barnard et al., 1993). Under the same conditions, the cyclo-oxygenase inhibitor, indomethacin, has no effect on the basal pulmonary vascular resistance of rats but increases pulmonary vascular resistance in dogs (Barnard et al., 1993). Thus, vasodilator prostaglandins regulate basal pulmonary vascular tone in the dogs, whereas NO regulates the basal pulmonary vascular tone in rats, cats, guinea pigs, pigs, and sheep. Basally released NO also plays an important role in the maintenance of low pulmonary vascular tone in humans (Celermajer et al., 1994; Stamler et al., 1994). Infusion of L-NMMA into healthy volunteers or children with congenital heart disease but with normal pulmonary blood flow, pressure, and resistance, causes a dose-dependent increase in pulmonary vascular resistance (Stamler et al., 1994), or decrease in pulmonary blood flow (Celermajer et al., 1994), with no change in PPA. Moreover, the increased PVR is associated with a reduction in plasma NO_3^- level (Stamler et al., 1994). Taken together with the demonstrations that basally released NO inhibits the contractile responses to adrenergic stimulation and other vasoconstrictors, these results indicate that basal NO plays an important role in the regulation of pulmonary vascular tone, both under basal conditions, and when tone is elevated. Basal NO release increases when PPA or vascular resistance is higher, thus providing a tonic antagonism to the elevation in pulmonary vascular tone and avoidance of any overshoot in pulmonary blood pressure.

B. Endothelium-Derived Hyperpolarizing Factor

EDHF may be another EDRF distinct from NO (Nagao and Vanhoutte, 1993) that causes the opening of a K^+ channel, leading to smooth muscle hyperpolarization. The nature of EDHF remains unknown, but its action is not inhibited by hemoglobin and methylene blue. EDHF has been reported in pulmonary artery (Chen et al., 1988). One complication for the understanding of EDHF is the demonstration that NO itself can open K^+ channels and causes hyperpolarization (Tare et al., 1990). Both exogenous NO and native EDRF can directly activate single Ca^{2+}-activated K^+ channels in cell-free membrane patches without requiring cGMP (Bolotina et al., 1994). Additionally, a specific inhibitor of K^+_{Ca} channels, charybdotoxin, virtually abolishes the methylene blue-resistant component in the NO-induced relaxation of rabbit aorta (Bolotina et al., 1994). The physiological role of EDHF is largely unexplored, but it seems to contribute to the endothelium-dependent relaxant responses to some vasodilators, such as ACh (Nagao and Vanhoutte, 1993).

C. Endothelium and Adrenergic Responses

Pulmonary vascular endothelium has an important modulatory role on the adrenergic response. Pulmonary endothelial cells take up and degrade norepinephrine, serotonin, and ATP, the principal transmitters and cotransmitters of adrenergic nerves, thereby diminishing the adrenergic contraction (Said, 1982). Endothelial cells activate and release vasoconstrictors, which may act synergistically with norepinephrine. More importantly, complex (*a*) endothelium-smooth muscle and (*b*) endothelium-adrenergic nerve interactions exist. Cocks and Angus (1983) observed a marked potentiation of the contractile response to norepinephrine and serotonin after removal of the vascular endothelium in canine and pig coronary arteries. Early studies showed that endothelium removal had no effect on the adrenergic contraction to either nerve stimulation (Loiacono and Story, 1984) or to exogenous norepinephrine in pulmonary vessels (de Mey and Vanhoutte, 1982), but more recent studies demonstrate a clear enhancement of the contractile response to adrenergic agonists (Greenberg et al., 1989; Crawley et al., 1990; Yamaguchi et al., 1989) and

to adrenergic nerve stimulation (Greenberg et al., 1989) in these vessels.

Several mechanisms have been explored. Endothelium-derived vasodilator prostaglandins are unlikely to be involved (Miller et al., 1984; Greenberg et al., 1989; Liu et al., 1991a). Reduction of norepinephrine degradation may play a role, but is unlikely to be important (Greenberg et al., 1989). In the isolated guinea pig pulmonary artery, electrical field stimulation (EFS) of intramural adrenergic nerves caused a frequency-dependent contraction, which was markedly enhanced by the NO synthase inhibitor L-NMMA in a concentration-dependent and L-arginine reversible manner, indicating endogenous NO is responsible for the endothelium-mediated inhibition (Liu et al., 1991a). An NO synthase inhibitor also augments the pressor response to sympathetic nerve stimulation in vivo (Tabrizchi and Triggle, 1991). An NO-adrenergic nerve interaction has also been suggested (Greenberg et al., 1989, 1990). In isolated dog intrapulmonary arteries and veins, endothelium removal enhances EFS-induced norepinephrine release (Greenberg et al., 1989). Basal effluent from endothelium-intact donor aorta inhibits EFS-induced norepinephrine release from denuded recipient pulmonary arteries (Greenberg et al., 1989).

NO-releasing compounds such as 3-morpholinosydnonime and nitroprusside inhibit norepinephrine release from perivascular adrenergic nerves of dog mesenteric arteries (Greenberg et al., 1990). However, NO synthase inhibitors have been consistently found to inhibit norepinephrine release in systemic vascular beds, suggesting that endogenous NO does not inhibit but rather facilitates norepinephrine release (Halbrugge et al., 1991; Yamamoto et al., 1993). The NO synthase inhibitor L-NMMA has no significant effect on EFS-induced norepinephrine release in guinea pig pulmonary arteries (Cederqvist et al., 1991).

Activation of endothelial α_2-adrenergic receptors leading to the release of NO from endothelial cells has been reported to be mainly responsible for the endothelium-mediated inhibition on adrenergic contraction in the vascular bed of skeletal muscles (Nakamura and Prewitt, 1991). Endothelial α_2-adrenoceptors exist in pulmonary vessels (Liu et al., 1991a). NO mediates α_2-adrenoceptor agonist-induced pulmonary vasodilation (Liu et al., 1991a; Pepke-Zaba et al., 1993). However, the α_2-adrenoceptor-mediated NO release is unlikely to be important in mediating the inhibitory effects of endothelium on adrenergic contraction in pulmonary vessels under physiological conditions (Liu et al., 1991a), inasmuch as norepinephrine has little relaxant effect on these vessels, even when the vascular tone was elevated (Liu et al., 1991a).

Under in vitro conditions, application of EFS activates intramural adrenergic, cholinergic, and NANC nerves simultaneously. NO is a transmitter of i-NANC nerves (Liu et al., 1992b) and a second-messenger molecule of cholinergic nerves (McMahon et al., 1992) in pulmonary vessels. NO released during the activation of these nerves could provide a functional antagonism to adrenergic contraction (Liu et al., 1992b). However, this mechanism may not be important under in vivo conditions, inasmuch as these nerves may not be activated simultaneously.

Both endothelial shear stress, caused by changes in perfusate velocity and viscosity, and mechanical deformation of vascular wall have been demonstrated to release EDRF/NO (Tesfamariam and Cohen, 1988; Lamontagne et al., 1992), and this NO also inhibits adrenergic contractions to EFS in systemic arteries (Tesfamariam and Cohen, 1988). This mechanism has not yet been confirmed in pulmonary vessels but presumably should be operative.

Although several factors contribute to the endothelium-mediated inhibition of adrenergic contraction, the basal and mechanically stimulated release of NO from endothelial cells are likely to be mainly responsible for the inhibition of adrenergic contraction. This could explain the uniform augmentation by NO synthase inhibitors of the contractile responses to vasoconstrictors with diverse mechanisms of action (Liu et al., 1991a). More recently, it was suggested that enhanced release of EDRF may contribute to the long-term α-adrenoceptor agonist exposure-induced desensitization of vascular smooth muscle to these agonists (Hu et al., 1994).

D. Endothelium and Cholinergic Responses

NO mediates ACh-induced vasodilation in the pulmonary circulation (McMahon et al., 1992). In the precontracted cat pulmonary vascular bed, vagal stimulation elicits a frequency-dependent relaxation, which is blocked by atropine and greatly inhibited by L-NAME and by inhibition of guanylyl cyclase. By contrast, L-NAME has no inhibitory effects on the dilator response to drugs with diverse mechanisms of action, including adenosine, nicorandil, isoproterenol, sodium nitroprusside, PGE_1, or 8-bromo-cGMP in the same preparation. There is still uncertainty about how ACh released from cholinergic nerve terminals at the adventitio-medial border exerts its action on endothelial cells, inasmuch as this presumably involves diffusion through the smooth muscle layer. Inconsistent results have been reported regarding the role of NO in mediating the relaxant response to exogenous ACh. NO synthase inhibitors inhibit the pulmonary vasodilator response to ACh in the cat and lamb in vivo (Fineman et al., 1991a; McMahon et al., 1991a, 1992) and in the blood-perfused rat pulmonary vascular bed in situ (Liu et al., 1991a) but do not significantly inhibit ACh-induced vasodilation in the physiological salt perfused pulmonary vascular bed of rat, although BK-induced relaxation was inhibited by the NO synthase inhibitor (Archer et al., 1989). The reason for this discrepancy is at present unclear.

E. Endothelium and Nonadrenergic, Noncholinergic Responses

The i-NANC vasodilator response in guinea pig is partially endothelium-dependent (Liu et al., 1992a). ATP, the possible i-NANC mediator, is an endothelium-dependent pulmonary vasodilator (Greenberg et al., 1987a; Liu et al., 1989a) and induces pulmonary vasodilation via stimulation of NO release from vascular endothelium (Liu et al., 1992a). As discussed in II.C.3, NO is likely to be an i-NANC neurotransmitter in pulmonary vessels (Liu et al., 1992b).

F. Endothelium and Humoral Mechanisms

Endothelial cells play an important role in the generation, metabolism, and degradation of many vasoactive substances. Pulmonary vascular endothelial cells take up and degrade vasoactive amines such as norepinephrine and serotonin (Alabaster and Bakhle, 1970; Said, 1982) and metabolize ATP to adenosine (Dieterle et al., 1978). Pulmonary endothelial cells contain angiotensin-converting enzyme, which catalyzes formation of A-II and degrades BK (Johnson and Erdös, 1977; Said, 1982) and tachykinins (Barnes et al., 1991). Endothelial cells also contain neutral endopeptidase to degrade enkephalin and other short peptides, including tachykinins (Erdös et al., 1978). Pulmonary endothelial cells participate in the metabolism of arachidonic acids (Said, 1982), and synthesize prostacyclin, a potent vasodilator and an inhibitor of platelet aggregation (Frangos et al., 1985). As discussed in V.A., endothelial cells also release NO, EDHF, and ET-1. These metabolic and secretory activities help to maintain homeostasis in the pulmonary circulation and to regulate pulmonary vascular smooth muscle tone.

Many vasoactive substances exert their pulmonary vasodilator actions via endothelium-dependent mechanisms, including histamine (Abacioglu et al., 1987), 5-HT (Glusa and Richter, 1993), BK (Ignarro et al., 1987a), ATP, ADP (Greenberg et al., 1987a; Liu et al., 1989a), substance P (Bolton and Clapp, 1986; Maggi et al., 1990), thrombin (De Mey and Vanhoutte, 1982) and arachidonic acid (De Mey and Vanhoutte, 1982). Another important mechanism for endothelium-dependent regulation of pulmonary vascular tone is shear stress-induced release of PGI_2 (Frangos et al., 1985). Both blood flow changes and mechanical deformation of the vascular wall impose shear stress on vascular endothelial cells and induce release of NO (Rubanyi et al., 1986; Lamontagne et al., 1992). Thus, an increase in pulmonary blood flow and possibly endothelium deformation due to pulmonary vasoconstriction will cause release of NO and PGI_2, which counteract the increase in pulmonary blood pressure. Activation of Ca^{2+}-activated K^+ channels seem to be involved in shear stress-induced NO release (Cooke et al., 1991).

G. Endothelium and Hypoxic Pulmonary Vasoconstriction

The pulmonary endothelium is an important modulator of HPV. Endothelial injury has been demonstrated to enhance HPV (Hill and Rounds, 1983; Rosenberg et al., 1985; Liu et al., 1992c) and hypoxic contractions (Tracey et al., 1989). Structural alterations in pulmonary endothelial cells may also contribute to the development of hypoxic pulmonary hypertension (Magee et al., 1988; Wilkinson et al., 1988). The pulmonary endothelium could modulate HPV by two mechanisms. Firstly, it metabolizes and clears several circulating vasoconstrictors, thereby reducing their synergistic action with hypoxia. Secondly, and more importantly, endothelial cells release potent vasodilators such as NO and PGI_2, which can inhibit the contractile response to hypoxia. Moreover, PGI_2 release is increased during HPV (Voelkel et al., 1981) and inhibition of PGI_2 synthesis by cyclooxygenase inhibitors enhances the pulmonary pressor response to hypoxia (Weir et al., 1976; Voelkel et al., 1981) and reduces blood flow perfusing hypoxic alveoli in a canine unilateral alveolar hypoxia model (Sprauge et al., 1984). Additionally, pulmonary arteries from rats exposed to hypoxia for 7 days have an almost three-fold elevation of PGI_2 compared with control animals (Shaul et al., 1991).

The modulatory role of EDRF on HPV was first demonstrated by Brashers et al. (1988), who showed a marked potentiation of HPV by nonselective EDRF inhibitors in perfused pulmonary vascular bed of rats. Subsequently, several groups reported marked augmentation of HPV to inhibit NO action, either by use of selective NO inhibitors (Archer et al., 1989; Liu et al., 1991b; Sprague et al., 1992) or guanylyl cyclase inhibitors (Mazmanian et al., 1989). The precursor of NO, L-arginine, has no effect on baseline pulmonary hemodynamics but inhibits and reverses HPV (Liu et al., 1991b; Fineman et al., 1991c). The effect of L-arginine on HPV is inhibited by methylene blue and potentiated by zaprinast, a PDE V inhibitor that inhibits cGMP degradation (Fineman et al., 1991c). Moreover, exogenous administration of NO and cGMP inhibits HPV (Frostell et al., 1991; Fujimoto et al., 1990; Roberts et al., 1993a). Thus, NO and PGI_2 act as functional antagonists to HPV, and loss of this feedback mechanism would potentiate hypoxia-induced contraction.

The role of suppression of EDRF activity in the mediation of HPV is uncertain. Low oxygen tension reduces NO synthase activity (Rengasamy and Johns, 1991) and reduces EDRF production from cultured bovine pulmonary vascular endothelial cells in response to BK (Warren et al., 1989). In addition, moderate (PO_2 = 40 mmHg) or severe (PO_2 = 4 to 17 mmHg) hypoxia inhibits endothelium-dependent relaxation to methacholine, ACh, ATP, and A23187 and the associated cGMP accumulation in rabbit and rat large pulmonary arteries

(Johns et al., 1989; Rodman et al., 1990) and in small pulmonary artery rings of sheep (Demiryurek et al., 1991), although this is not seen in isolated canine intrapulmonary arteries (Chand and Altura, 1981). In pig small pulmonary artery rings, hypoxia inhibits the relaxant response to ACh, reduces basal cGMP content, and augments the contractile response to phenylephrine, an effect that is abolished by endothelium removal (Ogata et al., 1992).

Hypoxic contraction is enhanced by removal of endothelium and by inhibition of NO using L-NMMA, hemoglobin, and methylene blue (Ogata et al., 1992). In isolated perfused bovine pulmonary artery and vein, both the activity and half-life of EDRF are *increased* by reduction in oxygen tension in the perfusate (Ignarro et al., 1988a). Differences in duration and severity of hypoxia or preconditions may explain these discrepancies. Nevertheless, these in vitro experiments may not be relevant to the physiological HPV response. These in vitro hypoxic contraction studies are conducted either on large conduit pulmonary arteries (Rodman et al., 1989; Johns et al., 1989; Rodman et al., 1990) or under conditions of severe hypoxia (Demiryurek et al., 1991; Ogata et al., 1992). Furthermore, this in vitro hypoxic contraction has been demonstrated in systemic arteries, including aorta (Furchgott and Zawadzki, 1980; Rodman et al., 1989), coronary arteries, (Graser and Vanhoutte, 1991; Muramatsu et al., 1992) and femoral arteries (de Mey and Vanhoutte, 1982), whereas HPV is unique to pulmonary vessels. The duration and degree of hypoxic exposure needed for elicitation of HPV (usually less than 10 minutes and PO_2 above 40 mmHg) are much shorter and of a lesser magnitude than those used in these in vitro studies. NO synthase activity may not be inhibited by moderate hypoxia. Additionally, even though the enzyme activity is inhibited to some extent, its activity may increase in response to strong stimuli. For example, hypoxia inhibits cyclo-oxygenase activity and PGI_2 production in rat pulmonary arteries in vitro (Shaul et al., 1992), whereas in vivo hypoxia results in a marked increase in tissue PGI_2 production (Shaul et al., 1991). During HPV, several factors, including endothelial shear stress resulting from changes in blood flow profile and endothelial deformation induced by smooth muscle contraction (Lamontagne et al., 1992), could stimulate EDRF release during acute HPV.

The effects of *chronic* hypoxia on endothelium-dependent responses are also controversial. Adnot et al. (1991b) reported that endothelium-dependent relaxant responses to ACh and A-23187 were diminished or abolished in the pulmonary vascular beds of rats exposed to hypoxia for 1 or 3 weeks. However, others observed enhanced dilator responses to ACh, BK, or A-23187 in the pulmonary vascular beds of rats and calves after exposure to chronic hypoxia (Barer et al., 1988; Orton et al., 1988; Russ and Walker, 1993); chronic hypoxia also does not inhibit basal EDRF activity (Oka et al., 1993; Barer et al., 1993). Large pulmonary arteries from hypoxic rats show an impaired relaxant response to ACh (Crawley et al., 1992c), although the relaxant response of the pulmonary vascular bed to sodium nitroprusside is unchanged by chronic hypoxia (Orton et al., 1988; Adnot et al., 1991b). Both unchanged and impaired relaxant responses to sodium nitroprusside have been reported in isolated large pulmonary rings from hypoxic calves (Orton et al., 1988) and rats (Crawley et al., 1992c; Wanstall and O'Donnell, 1992).

H. Endothelium in Immature Pulmonary Vessels

Endothelial cells may regulate fetal pulmonary vascular tone through the release of PGI_2 (Frangos et al., 1985). PGI_2 is a potent dilator of the fetal and perinatal pulmonary circulations (Leffler et al., 1979, 1980) and is released into the pulmonary circulation at birth (Leffler et al., 1980, 1984). Inhibition of PGI_2 synthesis slows down the reduction in PPA at birth (Leffler et al., 1978). The role of endothelium in the modulation of fetal pulmonary vascular tone has also been investigated. In pig pulmonary arteries, the relaxant response to ACh is negligible at birth (5 min to 2 h) but develops rapidly thereafter, becoming maximal at 3 to 10 days; the response decreases gradually, decreasing at 3 to 8 weeks, and becomes even lower in mature adults (Liu et al., 1992d; Zellers and Vanhoutte, 1991). Endothelium-dependent relaxant response to ACh and BK is absent in fetal rabbit pulmonary arteries (Zubrow et al., 1989) but exists in guinea pigs at age 1 to 3 days (Davidson and Eldemerdash, 1990).

In sheep, the relaxant responses to ACh or ATP are minimal in the fetus, increased in the newborn (1 to 4 weeks), and even greater in the adult pulmonary arteries (Abman et al., 1991). Using tissue cGMP content as an indicator of NO activity, Shaul et al. (1993) also demonstrated the existence of NO activity in the fetus, increased activity at 1 week, and even greater activity at 2 weeks. Maturational change in the sensitivity to ACh is also observed in the pulmonary veins of sheep (Steinhorn et al., 1993). The vasodilator response to ACh or BK is probably mediated predominantly by NO, inasmuch as L-NMMA and L-NA inhibit most of the relaxation (Liu et al., 1992d; Steinhorn et al., 1993). ACh-induced cGMP accumulation in fetal and neonatal pulmonary artery rings is also inhibited by L-NA (Shaul et al., 1993). However, the diminished response to ACh or BK in the fetal or neonatal pulmonary arteries is unlikely to be caused by a lack of sensitivity to NO, inasmuch as these vessels relax in response to sodium nitroprusside or NO to a similar extent as in neonatal or adult pulmonary arteries (Liu et al., 1992d; Steinhorn et al., 1993). Basal NO release in pulmonary vessels is greater at 1 day postnatally than at 7 days (Perreault and Marte, 1993).

The greater EDRF activity in neonates indicates that EDRF may be important in the second phase of pulmo-

nary vascular adaptation. The role of EDRF in the first phase of pulmonary vascular adaptation remains unclear. Endothelium-mediated relaxation to ACh and BK is absent in pulmonary arteries from fetal or early neonatal pigs and guinea pigs (Liu et al., 1992d; Zubrow et al., 1989) but is present, albeit small, in pulmonary arteries from fetal lambs (Abman et al., 1991; Shaul et al., 1993). In late gestational lambs, ACh causes an increase in pulmonary blood flow, which is inhibited by L-NA. L-NA elevates basal PPA and reduces the increase in pulmonary blood flow that occurs at birth (Abman et al., 1990); L-NA also inhibits the vasodilation induced by ventilation and increased oxygen tension in the lambs (Cornfield et al., 1992; Tiktinsky and Morin, 1993). Whether the difference between lamb and other species represents a species variation or reflects a difference between in vivo and in vitro studies is unclear. Additional in vivo studies to compare the maturational changes in EDRF activity are needed to answer this question.

I. Role of Endothelium in Pulmonary Vascular Disease

Inasmuch as endothelium represents one of the most important structures in the regulation of pulmonary vascular tone and vascular cellular functions, there has been considerable interest in the function and role of endothelial cells in pulmonary vascular diseases. Dysfunction and injury of pulmonary vascular endothelium may play an important role in the development of pulmonary hypertension (Loscalzo, 1992; Dinh-Xuan, 1993). Morphological changes of the intima have been observed in animal models of pulmonary hypertension, induced by administration of α-napthylthyiourea (Rounds et al., 1985), monocrotaline (Rosenberg et al., 1985; Kanai et al., 1993), endotoxin (Peach et al., 1989), and systemic-to-pulmonary arterial shunts (Esterly et al., 1968). Pulmonary endothelial structural changes are also found in patients with primary (Meyrick et al., 1974) and secondary pulmonary hypertension resulting from COPD (Magee et al., 1988; Wilkinson et al., 1988) and congenital heart defects (Rabinovitch et al., 1986). Pulmonary artery rings from patients with COPD and Eisenmenger's syndrome exhibit an impaired endothelium-dependent relaxant response (Dinh-Xuan et al., 1990, 1991).

Impairment of the pulmonary vasodilatory response to ACh has also observed in vivo in patients with primary (Conraads et al., 1993) and secondary pulmonary hypertension (Celermajer et al., 1993). This is in contradiction to most of the early reports that ACh and BK reduce PPA and/or PVR in patients with various types of pulmonary hypertension (Peach et al., 1989). Differences in the severity of disease may explain this discrepancy. The majority of these early studies did not compare ACh-mediated responses of hypertensive pulmonary vascular beds with those of normal pulmonary vascular beds. Another problem with in vivo assessment of endothelium-dependent responses is that pulmonary vasodilator response to most of the endothelium-dependent vasodilators are tone-dependent. A moderate reduction in endothelium-dependent relaxation could well be compensated by an increase in tone. Collectively, these results suggest that pulmonary vessels in pulmonary hypertension have an impaired endothelium-dependent response. Whether this impairment is a cause or a result of the disease is unclear. Nevertheless, endothelium-derived NO is an important inhibitory mechanism. Loss of this protective mechanism, reduction in NO and/or PGI_2 production, not only predisposes a patient to pulmonary vasoconstriction but may also facilitate the proliferation of pulmonary vascular smooth muscle cells.

NO-releasing agents and cGMP inhibit vascular smooth muscle mitogenesis and proliferation (Garg and Hassid, 1989). In cultured human umbilical vein endothelial cells, endogenous NO inhibits hypoxia-induced ET-1 and platelet-derived growth factor-β gene expression (Kourembanas et al., 1993). Moreover, endothelium-derived NO mediates heparin-induced inhibition on ET-1 production (Yokokawa et al., 1993) and the antiproliferation action of interferon-γ on vascular smooth muscle cells (Nunokawa and Tanaka, 1992). Loss of the endothelium-dependent inhibitory mechanism will facilitate the process of pulmonary vascular remodelling and thus accelerate the development of pulmonary hypertension.

Endogenous NO is also likely to be involved in septic shock (Stoclet et al., 1993), although the NO mediating the hypotension is probably derived predominantly from vascular smooth muscle cells and inflammatory cells (Nakayama et al., 1992; Liu et al., 1993, 1994b). Endothelial cells may also express the iNOS (Moncada et al., 1991; Stoclet et al., 1993) and therefore also contribute to the excess formation of NO. Down-regulation of eNOS may also play an important role in the early pulmonary hemodynamic changes during septic shock (Yoshizumi et al., 1993). The protective role of endogenous NO against neurogenic pulmonary edema (Liu et al., 1994a) suggests that NO may be of potential therapeutic benefit to patients with ARDS. Indeed, inhaled NO has been reported to attenuate pulmonary hypertension and improve gas exchange in animal models of septic ARDS (Weitzberg et al., 1993) and in ARDS patients with diverse underlying diseases (Gerlach et al., 1993).

VI. Second-messengers

A. Cyclic Nucleotides

Cyclic nucleotides are important in the regulation of pulmonary vascular tone. cGMP is the key second-messenger of NO-induced pulmonary vasodilation, whereas cAMP plays a central role in the pulmonary vasodilator response to many directly acting vasodilators, including β-adrenoceptor agonists, PGI_2, CGRP, and VIP. Exoge-

nous cGMP and cAMP themselves are potent pulmonary vasodilators (Haynes et al., 1992; McMahon et al., 1992, 1993a). The mechanism responsible for cGMP-induced vasodilation is incompletely understood but is related to activation of protein kinase G, inhibition of IP_3, dephosphorylation of myosin light chain kinase, stimulation of Ca^{2+}-ATPase, opening of K^+ channels, and inhibition of Ca^{2+} influx (Lincoln, 1989). Likewise, several mechanisms may mediate the vasodilator response to cAMP, including activation of cAMP-dependent protein kinase, resulting in a decreased myosin light chain kinase activity and reduced myosin phosphorylation, inhibition of Ca^{2+} influx, stimulation of Ca^{2+} efflux, and opening of Ca^{2+}-dependent K^+ channels (Murray, 1990). Inhibition of cGMP degradation by a cGMP specific (type V) PDE inhibitor decreases pulmonary perfusion pressure in constant perfused pulmonary vascular bed (McMahon et al., 1993a). In isolated endothelium-denuded pulmonary artery rings, there is a basal level of cGMP (Ignarro et al., 1987c). Both cAMP and cGMP modulate HPV and inhibit the development of hypoxic pulmonary hypertension. Stimulation of cAMP and cGMP formation inhibits pulmonary endothelial permeability to albumin and reduces pulmonary edema formation (Harada et al., 1989; Liu et al., 1994a), suggesting that cAMP and cGMP are protective against lung injury.

B. Phosphoinositide Hydrolysis

Activation of phospholipase C, resulting from stimulation of G-protein coupled receptors, leads to the hydrolysis of phosphoinositol bisphosphate-$_2$ and consequent generation of two second-messengers, IP_3 and 1,2-diacylglycerol. IP_3 mobilizes Ca^{2+} from intracellular stores, followed by the activation of Ca^{2+}/calmodulin-myosin light chain kinase, phosphorylation of myosin light chain, and vascular smooth muscle contraction (Berridge and Irvine, 1989), whereas 1,2-diacylglycerol activates PKC (see VI.C.). Many humoral substances and mediators affect pulmonary vascular tone via stimulation of G-protein coupled receptors (Birnbaumer, 1990). There is an increase in IP_3 generation with norepinephrine- but not hypoxia-induced contraction in isolated pulmonary artery, suggesting that IP_3 is not involved in hypoxic contraction of large pulmonary arteries (Jin et al., 1993).

C. Protein Kinases

Protein kinases play an important regulatory role in many physiological processes. As described above, cAMP-dependent protein kinase and cGMP-dependent protein kinase are involved in pulmonary vascular relaxation. Another protein kinase family, PKC is activated by 1,2-diacylglycerol and is present in high concentration in vascular smooth muscle (Kariya and Takai, 1987). PKC participates in the signal transduction process involved in excitation-contraction of pulmonary vascular smooth muscles, presumably via phosphorylation of substrates involved in the contractile process. Activation of PKC constricts isolated rat and human pulmonary artery rings (Orton et al., 1990; Savineau et al., 1991), and increases pulmonary perfusion pressure in perfused pulmonary vascular beds of rats (Orton et al., 1990; Michael et al., 1993). PKC activation also increases albumin permeability in bovine pulmonary vascular endothelial cell monolayers (Lynch et al., 1990) and inhibits isoproterenol-elicited cAMP production (Newman et al., 1989). All of these factors promote the formation of pulmonary edema. Indeed, PKC activators have been reported to cause pulmonary edema in rats and guinea pigs (Johnson, 1988; Perry and Taylor, 1988).

D. Calcium Channels

Changes in intracellular Ca^{2+} concentration $[Ca^{2+}]_i$ are critical in smooth muscle contraction or relaxation and the initiation of other cellular responses. The regulation of $[Ca^{2+}]_i$ involves a complex interaction between Ca^{2+} entry and extrusion across the plasmalemma and Ca^{2+} release and re-uptake from the sarcoplasmic reticulum. This Ca^{2+} movement is controlled mainly by Ca^{2+} channels. Two major classes of Ca^{2+} channels are expressed in vascular smooth muscle cells—voltage-dependent Ca^{2+} channels on the plasmalemma and intracellular Ca^{2+} release channels on the endoplasmic reticulum (Marks, 1992). There are several types of voltage-dependent Ca^{2+} channels, including L-type, T-type, N-type and P-type, which differ in structure, function, and pharmacological properties (Tsien et al., 1991). Voltage-dependent Ca^{2+} channels on vascular smooth muscle cells are usually of the L-type, whereas the release of intracellular Ca^{2+} is controlled by IP_3 receptors on sarcoplasmic reticulum (Marks, 1992).

There is little electrophysiological data regarding the Ca^{2+} channels or Ca^{2+}-currents in pulmonary vascular smooth muscle cells. Hypoxia reduces cell membrane potential, concomitant with contraction in small pulmonary artery rings of cats (Harder et al., 1985). It has been speculated that this is caused by a Ca^{2+}-dependent action potential (Harder et al., 1985). Evidence supporting this suggestion are the recent demonstration that hypoxia inhibits K^+ channel activity (both voltage-gated and Ca^{2+}-activated K^+ channels), induces depolarization of pulmonary artery smooth muscle cells—but not renal or mesenteric artery smooth muscle cells (Post et al., 1992; Yuan et al., 1993b; Cornfield et al., 1994)—and causes Ca^{2+} influx into cultured pulmonary artery smooth muscle cells of adult rats (Salvaterra and Goldman, 1993) and fetal lambs (Cornfield et al., 1994). Thus, it is possible that hypoxia inhibits K^+ channels, resulting in membrane depolarization of pulmonary smooth muscle cells, leading to the opening of Ca^{2+} channels and Ca^{2+} entry, which in turn results in contraction.

Functional studies also suggest that Ca^{2+} channels are important in the regulation of pulmonary vascular tone. Dihydropyridine Ca^{2+} antagonists inhibit HPV in animals in situ (McMurtry et al., 1976), in vivo (Tucker et al., 1976a; Young et al., 1983), and in human subjects (Simonneau et al., 1981; Burghuber, 1987). BAY K 8644, a dihydropyridine Ca^{2+} agonist, has no effect on basal pulmonary perfusion pressure but markedly enhances hypoxic pulmonary vasoconstriction (McMurtry, 1985). Ca^{2+} antagonists also inhibit, and BAY K 8644 potentiates, the constrictor response to A-II or $PGF_{2\alpha}$. However, the effect on HPV is much greater than on A-II contraction, suggesting that HPV is more dependent on extracellular Ca^{2+} (McMurtry et al., 1976; McMurtry, 1985).

E. Potassium Channels

Membrane depolarization and hyperpolarization, through inhibition and activation of K^+ channels, respectively, are important mechanisms regulating smooth muscle contraction and relaxation. The development of selective K^+ channel openers has facilitated investigation into the role of K^+ channels in the control of pulmonary vascular tone and in pulmonary vascular physiology. Several types of K^+ channels have been identified and cloned (Pongs, 1992; Quast, 1993). Most of these channels are present in vascular smooth muscle cells (Kajioka et al., 1991). K^+ channels described on pulmonary vascular smooth muscles include voltage-gated K^+ channels (Yuan et al., 1993a, b), Ca^{2+}-activated K^+ channels (Lee et al., 1991b; Robertson et al., 1992), including large conductance Ca^{2+}-activated K^+ channels (Kirber et al., 1992), delayed rectifier channels (Okabe et al., 1987; Smirmov et al., 1994) and ATP-sensitive K^+ channels (Clapp and Gurney, 1992).

Activation of K_{ATP} channels relaxes precontracted pulmonary vessel rings in vitro (Clapp et al., 1993; Savineau and Marthan, 1993), pulmonary vascular beds in situ (Hood et al., 1991a, b), and pulmonary vascular beds under basal conditions in vivo (Minkes et al., 1991; Chang et al., 1992). K_{ATP} channel activation also reverses HPV, causes pulmonary vascular hyporeactivity to other vasoconstrictors (Savineau and Marthan, 1993), and mediates pulmonary vasodilatory response to severe hypoxia (Wiener et al., 1991). It is reported that chronic hypoxia for 72 h augments K_{ATP} channel mediated relaxation in the rat pulmonary vascular bed (Rodman, 1992). Smooth muscle cells isolated from small pulmonary arteries of rats exposed to chronic hypoxia show a reduced resting membrane potential, suggesting a partial depolarization (Smirnov et al., 1994). Both delayed rectifier and K^+_{ATP} channels are involved in this depolarization (Smirnov et al., 1994).

Voltage-gated K^+ channel activity on cultured pulmonary artery smooth muscle cells is inhibited by hypoxia and has been implicated in hypoxic contraction (Yuan et al., 1993b) or HPV (Post et al., 1992). Voltage-gated or Ca^{2+}-activated K^+ channels may contribute to the maintenance of basal pulmonary vascular tone (Hasunuma et al., 1991b). In human small pulmonary arteries, K_{ATP} channels mediate the dilator response to K^+ channel openers, such as levacromakalim, whereas the large conductance Ca^{2+}-activated K^+ channel that is blocked by charybdotoxin is involved in the relaxation response to nitroprusside (Crawley et al., 1992b). Vascular endothelial cells also contain various K^+ channels (Revest and Abbott, 1992). Ca^{2+}-activated K^+ channels are involved in the shear stress-induced release of NO in systemic arteries (Cooke et al., 1991), although this mechanism has not been demonstrated in pulmonary vessels.

VII. Pulmonary Vasodilators as Therapy

A. General Principles

The rationale for treating pulmonary hypertension with vasodilators was stimulated by the successful application of vasodilator therapy to systemic hypertension, and virtually every vasodilator agent has been investigated. There has been a search for drugs that vasodilate the pulmonary circulation without lowering the systemic blood pressure and cardiac output to an extent that causes side effects. Unfortunately, most pulmonary vasodilators have been unsuccessful, either because of therapeutic failure or intolerable side effects. A few drugs, such as hydralazine, PGI_2, and Ca^{2+}-channel blockers, have been the most promising vasodilator drugs, with effective reduction of PPA with relatively little reduction in systemic arterial pressure or resistance and an increase in cardiac output in some patients (Rich et al., 1983a). Additionally, vasodilator therapy with these agents may improve survival over 5 years and improve the quality of life (Beltran Gamez et al., 1988; Rich et al., 1992). However, these drugs are not selective for the pulmonary circulation. At present, the only available selective pulmonary vasodilator is oxygen. Recently, acute infusion of adenosine and inhalation of NO gas have been shown to reduce pulmonary vascular resistance, without obvious effects on SVR and cardiac output (Morgan et al., 1991b; Pepke-Zaba et al., 1991). Additionally, adenosine has been shown to be additive to Ca^{2+}-channel blockers in dilating pulmonary vascular beds of patients with PPH (Ihbar et al., 1993).

B. Hydralazine

Most clinical studies on the effectiveness of hydralazine in pulmonary hypertension were conducted in the 1980s with small numbers of subjects and provided conflicting results. Rubin and Peter (1980) reported that oral hydralazine effectively reduced PVR at rest and during exercise in four patients with PPH. The reduction in PRV was sustained with chronic oral therapy. They also showed a reduction in right ventricular end-diastolic pressure and improved right ventricular function (Rubin et al., 1982a). However, others failed to confirm the beneficial effect of hydralazine and even

showed deleterious effects (Packer et al., 1982; Rich et al., 1983b; Fisher et al., 1984). The reason for this inconsistency may relate to the severity of the disease or differences in individual responsiveness.

Lupi-Herrera et al. found that their 12 patients with PPH could be divided into responders and nonresponders (6 patients in each group). Responders had lower pulmonary pressure and PVR, whereas nonresponders had higher PPA and a higher PVR. Responders showed a beneficial pulmonary hemodynamic responses, both acutely and chronically, up to 8 months (Lupi-Herrera et al., 1982).

Hydralazine was also used in patients with hypoxic pulmonary hypertension, with similarly controversial results. Some reported that hydralazine was beneficial, with reduction in PPA, improved cardiac index, oxygen transport, alveolar ventilation, and exercise tolerance (Keller et al., 1984; Lupi-Herrera et al., 1985; Corriveau et al., 1987). Other investigators found that hydralazine had no beneficial effects on these patients (Tuxen et al., 1984; Cerda et al., 1985; Dal Nogare and Rubin, 1986). Beltran Gamez et al. (1988) analyzed the long-term effects of vasodilator therapy in 40 patients with PPH who received hydralazine or nifedipine and had been followed for an average of 50 ± 8 months. Twenty were classified as responders and 20 as nonresponders. The 5-year probability of survival was 86% and 45% for responders and nonresponders, respectively, although these two figures are not comparable, inasmuch as the two groups had different basal hemodynamic profiles. However, most of the responders (13 with nifedipine, 7 with hydralazine) showed a significant improvement in their quality of life and maintained a good hemodynamic response during the period of follow-up (Beltran Gamez et al., 1988).

C. Calcium-Channel Blockers

Ca^{2+}-channel blockers are the most widely used pulmonary vasodilators. In a review of reports published between 1978 and 1985 of vasodilator therapy in the treatment of PPH, 45 of the 117 reported patients were treated with Ca^{2+}-channel blockers (Reeves et al., 1986). Several Ca^{2+}-channel blockers, including verapamil, diltiazem, felodipine, nisoldipine, and bepridil have been tested, although nifedipine was the most extensively evaluated. Nifedipine has been used in PPH (Rubin, 1985; Reeves et al., 1986), pulmonary hypertension secondary to COPD (Michael et al., 1985; Rubin et al., 1986), systemic sclerosis (Ohar et al., 1985), interstitial lung disease (Ohar et al. 1985), chronic thromboembolism (Galie et al., 1985), obliterative pulmonary vascular disease (Packer et al., 1984), bronchopulmonary dysplasia (Brownlee et al., 1988), and congenital heart disease (Wimmer at al., 1988). The majority of these reports obtained favorable results, with the exceptions of patients with chronic thromboembolic pulmonary hypertension and congenital heart disease, for whom either a worsening or an equivocal pulmonary hemodynamic response was observed after nifedipine (Galie et al., 1985; Wimmer et al., 1988). Acute administration of nifedipine, either orally or sublingually, (*a*) lowers PPA, PVR, or both, (*b*) increases cardiac output, (*c*) improves right ventricular function, and (*d*) improves exercise tolerance (Rubin, 1985; Michael et al., 1985; Reeves et al., 1986). Although nifedipine results in some deterioration of V/Q matching, PaO_2 is unchanged or slightly increased or decreased. O_2 delivery is increased. Nifedipine also reduces systemic blood pressure, SVR, or both to a tolerable extent in the majority of patients. Nifedipine therapy is also effective in PPH. Rubin et al. (1983) first reported favorable effects in 6 patients with PPH treated with oral nifedipine for 4 to 14 months. In two uncontrolled trials, a total of 21 patients with PPH were followed for more than 1 year; there was a general improvement in pulmonary hemodynamics and symptoms without any intolerable side effects in 14 patients (Rich et al., 1985; Khossein et al., 1988). A recent large-scale, controlled clinical trial showed that a sustained reduction in PPA and PVR and improvement of survival over a period of 5 years can be achieved in PPH patients who have a favorable initial response to acute nifedipine (Rich et al., 1992).

There are concerns about the side effects of Ca^{2+}-channel blockers in the treatment of PPH. In 1985, a case of severe pulmonary edema in a patient with PPH given nifedipine was reported (Batra et al., 1985), and recently, nifedipine was reported to contribute to the death of a 17-year-old patient with PPH (Partanen et al., 1993). Thus, appropriate assessment and an acute response test should be carried out before starting long-term, high-dose Ca^{2+}-blocker therapy. Because Ca^{2+}-channel blockers inhibit HPV very effectively in both animals and human subjects (Kennedy et al., 1984; Michael et al., 1984), nifedipine is also widely used in the treatment of hypoxic pulmonary hypertension. Nifedipine (*a*) lowers PPA, PVR, or both, (*b*) increases cardiac output, and (*c*) improves exercise tolerance in these patients (Gassener et al., 1986; Morley et al., 1987; Gassener et al., 1990). Nifedipine lowers PVR to a greater extent than SVR and increased O_2 delivery in patients with COPD (Gassener et al., 1986; Saadjian et al., 1987). PaO_2 is reduced (Saadjian et al., 1987) or unchanged (Morley et al., 1987; Mookherjee et al., 1988) by nifedipine. However, in contrast to its acute beneficial effects, nifedipine does not have long-term beneficial effects in these patients. Two large-scale, controlled trials showed no difference in either pulmonary hemodynamics or survival rate in the long-term nifedipine treatment group after a follow-up period of 12 to 18 months (Vestri et al., 1988; Saadjian et al., 1988). Several studies have demonstrated that nifedipine causes a significant reduction in both PPA and PRV when given acutely but has no effect on pulmonary hemodynamics in the same groups of patients when given as long-term treat-

ment (Morley et al., 1987; Mookherjee et al., 1988; Gassner et al., 1990). Interestingly, a Chinese herbal remedy, ligustrazine, used to treat cardiovascular diseases, relaxes human pulmonary vessels in vitro, probably by acting as a Ca^{2+} antagonist (Liu et al., 1990).

D. Prostacyclin

PGI_2 is not only a potent vasodilator but also an antiplatelet aggregatory agent. PGI_2 has no selectivity for pulmonary vessels. Early studies showed that acute infusion of PGI_2 into pulmonary circulation through a pulmonary artery catheter reduced PVR and SVR to a similar extent, with a marked increase in cardiac output (Rubin et al., 1982b; Groves et al., 1985; Bush et al., 1985). The advantage of PGI_2 over other vasodilators is its half-life of minutes, providing greater control over systemic effects. Clinical studies indicate that it can effectively reduce PVR with tolerable side effects (Rubin et al., 1982b; Grove et al., 1985; Jones et al., 1987) and that it is very effective in relieving pulmonary hypertensive crises in PPH (Scott et al., 1991). PGI_2 also improves O_2 delivery in these patients (Jones et al., 1987). PGI_2 has been reported be equally effective to nifedipine (Barst, 1986) but has a better pulmonary vasodilator action than tolazoline (Bush et al., 1988).

PGI_2 is additive with oxygen therapy in patients with pulmonary hypertension secondary to congenital heart disease (Bush et al., 1986). There is a report that PGI_2 is ineffective in PPH (Guadagni et al., 1981), but this may reflect a difference in individual responses to this drug. In a study of nine patients aged 9 months to 23 years with pulmonary hypertension secondary to congenital heart disease, Barst (1986) found five responders and four nonresponders, using a 20% fall in P_{PA}, an increase in cardiac index, and no change in PVR: SVR ratio as criteria. All the nonresponders also failed to respond to nifedipine. This feature and its short half-life provide the basis for the use of PGI_2 as a predictor in assessing pulmonary vascular reactivity to long-term vasodilator treatment and for heart-lung transplantation (Rozkovec et al., 1988; Jones et al., 1989; Palevsky et al., 1990).

PGI_2 is very effective in the acute treatment of postoperative pulmonary hypertension associated with pulmonary edema (Pascual et al., 1990; Schranz et al., 1992) and allograft failure (Esmore et al., 1990), and pulmonary hypertension complicating various types of ARDS (Radermacher et al., 1990; Clarke, 1990). Long-term infusion of PGI_2 is also used to treat PPH (Higenbottam et al., 1984). A randomized clinical trial in patients with PPH shows that chronic infusion of PGI_2 produces a substantial and sustained reduction in PVR (Rubin et al., 1990). However, chronic infusion is expensive, and there is a risk of infection.

E. Oxygen

Hypoxemia is always seen in patients with pulmonary hypertension secondary to COPD and contributes to the poor prognosis of these patients. Numerous studies have indicated that correction of this hypoxemia using long-term oxygen therapy reduces P_{PA}, decreases erythrocytosis, and improves exercise tolerance and neuropsychological function (Medical Research Council Working Party, 1981; Nocturnal Oxygen Therapy Trial Group, 1980). Two large-scale, controlled clinical trials involved 203 and 87 patients with COPD (Nocturnal Oxygen Therapy Trial Group, 1980; Medical Research Council Working Party, 1981), and one retrospective analysis involving 127 COPD patients (Miyamoto et al., 1992); all indicate that long-term oxygen therapy prolongs life expectancy and the quality of life in these patients. Neither of the two earlier trials showed a reduction in P_{PA}. However, a later trial by the Nocturnal Oxygen Therapy Trial Group showed that hemodynamic responses to long-term oxygen therapy over a period of 3 to 6 months related to survival, suggesting that the pulmonary vascular response is an important factor (Timms et al., 1985). Hypoxic patients with a reduction in P_{PA} in response to breathing O_2 (responder) showed a much higher rate of survival than did nonresponders (Ashutosh and Dunsky, 1987). A postmortem investigation revealed no difference in pulmonary vascular structures between responders and age- and P_{PA}-matched nonresponders (Wright et al., 1992). These results indicate that HPV is likely to be an important component of hypoxic pulmonary hypertension. Accumulating evidence indicates that long-term oxygen therapy reduces P_{PA}, prevents nocturnal arterial desaturation and its associated P_{PA} elevation (Geraads et al., 1984), and reverses the progression of pulmonary hypertension (Weitzenblum et al., 1985; Weitzenblum et al., 1989).

Oxygen is also an effective pulmonary vasodilator in other forms of pulmonary hypertension. There are scattered reports that oxygen inhalation reduced P_{PA}, PVR, or both in PPH (Nagasaka et al., 1978) and that pulmonary hypertension was caused by pulmonary thromboembolic disease (Dantzker and Bower, 1981), congenital heart disease (Bush et al., 1985), bronchopulmonary dysplasia (Palmisano et al., 1990), systemic sclerosis (Morgan et al., 1991a), and pulmonary hypertension associated with liver cirrhosis (Tabuchi et al., 1990). Failure to reduce P_{PA} or PVR by using oxygen has also been reported in patients with PPH (Morgan et al., 1991a).

F. Nitric Oxide

NO is a potent pulmonary vasodilator and has a short half-life, making it an attractive treatment option for pulmonary hypertension as an inhaled therapy (Pearl, 1993). In awake lambs, spontaneous breathing of NO at 40 to 80 parts per million reversed pulmonary hypertension induced by either hypoxia or infusion of a thromboxane mimetic, without affecting systemic hemodynamics (Frostell et al., 1991). Inhalation of 40 parts per million of NO in air was demonstrated to markedly

reduce PVR, without effects on SVR in patients with secondary pulmonary hypertension, whereas infusion of PGI_2 reduced both PVR and SVR (Pepke-Zaba et al., 1991). These results suggest that inhaled NO is a selective pulmonary vasodilator.

Inhaled NO therapy was subsequently applied to the treatment of ARDS (Weizberg et al., 1993; Rossiant et al., 1993; Gerlach et al., 1993), pulmonary hypertension secondary to congenital heart disease (Roberts et al., 1993b; Berner et al., 1993) and acquired heart disease (Girard et al., 1992), infant persistent pulmonary hypertension (Roberts et al., 1992; Kinsella et al., 1992), COPD (Adnot et al., 1993; Adatia et al., 1993b), pneumonia (Blomqvist et al., 1993) and used during cardiac surgery (Rich et al., 1993). These studies show that inhaled NO is a selective pulmonary vasodilator and improves gas exchange, particularly in patients with ARDS. The explanation for the paradoxical reversal of HPV and improvement of pulmonary capillary gas exchange is that inhaled NO reaches only the well-ventilated lung regions and thereby improves the ventilation/perfusion matching, thus facilitating gas exchange (Quinn and Vallance, 1993). Inhaled NO is also a bronchodilator in animals (Dupuy et al., 1992) and humans (Högman et al., 1993), and this may also contribute to the improved gas exchange in some patients. The main advantages of inhaled NO therapy are its efficacy, cheapness, and selectivity for the pulmonary circulation. However, there are some concerns about toxicity, inasmuch as high concentrations of NO are toxic (Beackman et al., 1990; Wink et al., 1991) and interact with hemoglobin to form methemoglobin, resulting in methemoglobinemia. Additional studies are needed to establish the therapeutic range, particularly when repeated inhalations are used (Gerlach et al., 1993; Rich et al., 1993). Moreover, NO has different redox forms under different conditions and exerts its toxic actions through different mechanisms (Stamler et al., 1992), emphasizing the need to obtain more detailed time course and dose-response relationships under various pathophysiological conditions. Additionally, randomized controlled trials are now required to study the effect of inhaled NO on long-term survival and morbidity.

G. Future Therapies

The selectivity of inhaled NO, compared with other vasodilators, has raised the question of whether selectivity of pulmonary vasodilation can be achieved by giving other vasodilators via the inhaled route. This may be applied to PGI_2, Ca^{2+} antagonists, K^+-channel openers, and adenosine. The rationale for using vasodilators is the reversal of an increase in pulmonary vascular smooth muscle contraction, but these drugs have no direct effect on pulmonary vascular remodelling (although lowering PVR may slow down or reverse the remodelling). This has suggested that new treatments should target the prevention and reversal of structural changes caused by fibrosis and hyperplasia of vascular smooth muscle. The marked increase in ET-1 immunoreactivity in the pulmonary vessels of patients with primary and secondary pulmonary hypertension (Giaid et al., 1993) suggests that ET-antagonists may be useful as therapy in the future (Barnes, 1994). Recently, nonpeptide orally active ET-antagonists have become available and might be indicated in the treatment of pulmonary hypertension (Clozel et al., 1993), inasmuch as ET-antagonists inhibit the progress of pulmonary hypertension in experimental animals (Miyauchi et al., 1993) and inhibit the proliferation of pulmonary vascular smooth muscle in vitro (Zamora et al., 1993b).

VIII. Conclusions and Future Perspectives

The pulmonary circulation is regulated by a complex network of neural and humoral factors that interact with the passive forces imposed on this low-pressure system from the systemic circulation. These factors result in optimal matching of pulmonary perfusion to ventilation in order to maintain normoxia. There is much evidence indicating that the endothelium plays a critical role in regulating pulmonary vascular tone, and dysfunction of pulmonary endothelial cells may play an important role in pulmonary vascular disease (Liu and Barnes, 1994). There is increasing interest in the molecular mechanisms involved in the secretion of endothelial mediators, and the pathways involved seem to be complex. Several factors may influence the expression of surface receptors, intracellular signalling pathways, and gene expression in these cells and thus may influence pulmonary vascular tone. Pulmonary vascular smooth muscle is also subject to many influences, and it is now becoming apparent that these cells are metabolically active and may release mediators and cytokines that influence their tone. Both endothelial cells and smooth muscle cells release mediators that have effects on the extracellular matrix of the vessel. The extracellular matrix is actively maintained, and the remodelling that occurs in chronic pulmonary disease is an important component of vascular resistance that may be difficult to reverse.

Despite intense investigation, HPV remains something of a mystery. It is still unclear why small pulmonary arteries have the opposite response from that of systemic vessels. While endothelial cells clearly have the capacity to modulate HPV and may play a modulatory role, it is likely that pulmonary vascular smooth muscle cells themselves hold the key to the mechanism. It has proved difficult to isolate and study these smooth muscle cells, and studies of vascular smooth muscle cells from other vessels may be misleading. Similarly, it is difficult to isolate and culture endothelial cells from these vessels.

Chronic influences on pulmonary vessels have been more difficult to study at a cellular level, but the application of molecular probes and the use of antisense oli-

gonucleotides in vivo may help to elucidate the molecular pathways involved in chronic pulmonary vascular diseases in the future.

The long-term therapy of pulmonary hypertension is still unsatisfactory because of the difficulty in selectively reducing pulmonary vascular resistance without affecting the systemic circulation. The recent demonstration that inhaled NO effectively lowers pulmonary vascular pressures is of great interest, as this shows the validity of an approach where a drug selectively targets the pulmonary circulation. In the case of NO, this is because it is not able to reach the systemic circulation because of its rapid combination with hemoglobin, and this is therefore a special case (Pearl, 1993). Intravenous adenosine also shows some selectivity for the pulmonary circulation, again because it is so rapidly metabolized in the systemic circulation (Morgan et al., 1991b). However, while these treatments are useful in the acute reduction of pulmonary vascular pressures, they are not suited to long-term use in ambulant patients. Oxygen should also be considered as a selective pulmonary vasodilator, as it reverses HPV and has no effect on the systemic circulation. Long-term oxygen therapy is indicated for patients who have pulmonary hypertension secondary to COPD, but it must be taken for more than 12 h each day and is not indicated for other forms of pulmonary hypertension. It is possible that delivery of drugs via the inhaled route may achieve some selectivity, and this approach should be exploited using optimal lung delivery systems. It is hoped that, in the future, it will be possible to develop more selective pulmonary vasodilators, and such drugs may emerge from more detailed pharmacological studies of the pulmonary circulation.

REFERENCES

ABACIOGLU, N., ERCAN, Z. S., KANZIK, L., ZENGIL, H., DEMIRYUREK, T., AND TURKER, R. K.: Endothelium-dependent relaxing effect of histamine on the isolated guinea-pig main pulmonary artery strips. Agents Actions **22:** 30–35, 1987.

ABDELRAHMAN, A., WANG, Y-X., CHANG, S. D., AND PANG, C. Y.: Mechanism of the vasodilator action of calcitonin gene-related peptide in conscious rats. Br. J. Pharmacol. **106:** 45–48, 1992.

ABELL, T. J., RICHARDS, A. M., IKRAM, H., ESPINER, E. A., AND YANDLE, T.: Atrial natriuretic factor inhibits proliferation of vascular smooth muscle cells stimulated by platelet-derived growth factor. Biochem. Biophys. Res. Commun. **160:** 1392–1396, 1989.

ABMAN, S. H., CHATFIELD, B. A., HALL, S. L., AND MCMURTRY, I. F.: Role of endothelium-derived relaxing factor during transition of the pulmonary circulation at birth. Am. J. Physiol. **259:** H1921–H1927, 1990.

ABMAN, S. H., CHATFIELD, B. A., RODMAN, D. M., HALL, S. L., AND MCMURTRY, I. F.: Maturational changes in endothelium-derived relaxing factor activity of ovine pulmonary arteries in vitro. Am. J. Physiol. **260:** L280–L285, 1991.

ADATIA, I., BARROW, S. E., STRATTON, P. D., MIALL-ALLEN, V. M., RITTER, J. M., AND HAWORTH, S. G.: Thromboxane A_2 and prostaglandin biosynthesis in children and adolescents with pulmonary vascular disease. Circulation **88:** 2117–2122, 1993a.

ADATIA, I., THOMPSON, J., LANDZBERG, M., AND WESSEL, D. L.: Inhaled nitric oxide in chronic obstructive lung disease. Lancet **341:** 307–308, 1993b.

ADNOT, S., ANDRIVET, P., CHABRIER, P. E., PIQUET, J., PLAS, P., BRAQUET, P., ROUDOT-THORAVAL, F., AND BRUN-BUISSON, C.: Atrial natriuretic factor in chronic obstructive lung disease with pulmonary hypertension. Physiological correlates and response to peptide infusion. J. Clin. Invest. **83:** 986–993, 1989.

ADNOT, S., CHABRIER, P. E., ANDRIVET, P., VIOSSAT, I., PIQUET, J., BRUN-BUISSON, C., GUTKOWSKA, Y., AND BRAQUET, P.: Atrial natriuretic peptide concentrations and pulmonary hemodynamics in patients with pulmonary artery hypertension. Am. Rev. Respir. Dis. **136:** 951–956, 1987.

ADNOT, S., CHABRIER, P. E., BRUN-BUISSON, C., VIOSSAT, I., AND BRAQUET, P.: Atrial natriuretic factor attenuates the pulmonary pressor response to hypoxia. J. Appl. Physiol. **65:** 1975–1983, 1988.

ADNOT, S., CIGARINI, I., HERIGAULT, R., AND HARF, A.: Effects of substance P and calcitonin gene-related peptide on the pulmonary circulation. J. Appl. Physiol. **70:** 1707–1712, 1991a.

ADNOT, S., KOUYOUMDJIAN, C., DEFOUILLOY, C., ANDRIVET, P., SEDIAME, S., HERIDAULT, R., AND FRATACCI, M-D.: Hemodynamic and gas exchange responses to infusion of acetylcholine and inhalation of nitric oxide in patients with chronic obstructive lung disease and pulmonary hypertension. Am. Rev. Respir. Dis. **148:** 310–316, 1993.

ADNOT, S., RAFFESTIN, B., EDDAMIBI, S., BRAQUET, P., AND CHABRIER, P. E.: Loss of endothelium-dependent relaxant activity in the pulmonary circulation of rats exposed to chronic hypoxia. J. Clin. Invest. **87:** 155–162, 1991b.

AHLNER, J., LJUSEGREN, M. E., GRUNDSTROM, N., AND AXELSSON, K. L.: Role of nitric oxide and cyclic GMP as mediators of endothelium-independent neurogenic relaxation in bovine mesenteric artery. Circ. Res. **68:** 756–762, 1991.

AHMAD, S., CHRETIEN, P., DANIEL, E. E., AND SHEN, S. H.: Characterization of beta adrenoceptors on cultured endothelial cells by radioligand binding. Life Sci. **47:** 2365–2370, 1990.

AHMED, T., MARCHETTE, B., WANNER, A., AND YERGER, L.: Direct and indirect effects of leukotriene D_4 on the pulmonary and systemic circulations. Am. Rev. Respir. Dis. **131:** 554–558, 1985.

AHMED, T., WASSERMAN, M. A., MUCCITELLI, R., TUCKER, S., GAZEROGLU, H., AND MARCHETTE, B.: Endotoxin-induced changes in pulmonary hemodynamics and respiratory mechanics: role of lipoxygenase and cyclooxygenase products. Am. Rev. Respir. Dis. **134:** 1149–1157, 1986.

ALABASTER, V. A., AND BAKHLE, Y. S.: Removal of 5-hydroxyltryptamine in the pulmonary circulation of rat lungs. Br. J. Pharmacol. **40:** 468–482, 1970.

ALBERT, R. K., LAMM, W. J., HENDERSON, W. R., AND BOLIN, R. W.: Effect of leukotrienes B_4, C_4, and D_4 on segmental pulmonary vascular pressures. J. Appl. Physiol. **66:** 458–464, 1989.

ALLGAIER, C., PULLMANN, F., AND SCHOBERT, A.: P_2 purinoceptors modulating noradrenaline release from sympathetic neurons in culture. Eur. J. Pharmacol. **252:** R7–R8, 1994.

ANAND-SRIVASTAVA, M. B., AND TRACHTE, G. J.: Atrial natriuretic factor receptors and signal transduction mechanisms. Pharmacol. Rev. **45:** 455–497, 1993.

BAERTSCHI, A. J., AND TEAGUE, W. G.: Alveolar hypoxia is a powerful stimulus for ANP release in conscious lambs. Am. J. Physiol. **256:** H990–H998, 1989.

ANDERSON, F. L., AND BROWN, A. M.: Pulmonary vasoconstriction elicited by stimulation of the hypothalamic integrative area for the defense reaction. Circ. Res. **21:** 747–756, 1967.

ARCHER, S. L., HUANG, J., HENRY, T., PETERSON, D., AND WEIR, E. K.: A redox-based sensor in rat pulmonary vasculature. Circ. Res. **73:** 1100–1112, 1993.

ARCHER, S. L., KULIK, T. J., CHESLER, E., AND WEIR, E. K.: The effects of substance P on the preconstricted pulmonary vasculature of the anesthetized dog. Proc. Soc. Exp. Biol. Med. **183:** 19–27, 1986a.

ARCHER, S. L., TOLINS, J. P., RAIJ, L., AND WEIR, E. K.: Hypoxic pulmonary vasoconstriction is enhanced by inhibition of the synthesis of an endothelium-derived relaxing factor. Biochem. Biophys. Res. Commun. **164:** 1198–1205, 1989.

ARCHER, S. L., WILL, J. A., AND WEIR, E. K.: Redox status in the control of pulmonary vascular tone. Herz **11:** 127–141, 1986b.

ARNAL, J-F., WARIN, L., AND MICHEL, J-B.: Determinants of aortic guanosine monophosphate in hypertension induced by chronic inhibition of nitric oxide synthase. J. Clin. Invest. **90:** 647–652, 1992.

ASHUTOSH, K., AND DUNSKY, M.: Noninvasive tests for responsiveness of pulmonary hypertension to oxygen. Prediction of survival in patients with chronic obstructive lung disease and cor pulmonale. Chest **92:** 393–399, 1987.

AVIADO, J., LING, J. S., AND SCHMIDT, C. F.: Effects of anoxia on pulmonary circulation: reflex pulmonary vasoconstriction. Am. J. Physiol. **189:** 253–262, 1957.

BAERTSCHI, A. J., AND TEAGUE, W. G.: Alveolar hypoxia is a powerful stimulus for ANP release in conscious lambs. Am. J. Physiol. **256:** H990–H998, 1989.

BARER, G. R.: Reactivity of the vessels of collapsed and ventilated lungs to drugs and hypoxia. Circ. Res. **18:** 336, 1966.

BARER, G. R.: Active control of the pulmonary circulation. *In* Pulmonary Circulation in Health and Disease, ed. by G. Cumming and G. Bonsignore, pp. 81–124, Plenum Press, New York, 1980.

BARER, G. R., CAI, Y. N., RUSSELL, P. C., AND EMERY, C. J.: Reactivity and site of vasomotion in pulmonary vessels of chronically hypoxic rats: relation to structural changes. Am. Rev. Respir. Dis. **140:** 1483–1485, 1988.

BARER, G., EMERY, C., STEWART, A., BEE, D., AND HOWARD, P.: Endothelial control of the pulmonary circulation in normal and chronic hypoxic rats. J. Physiol. (Lond.) **463:** 1–16, 1993.

BARMAN, S. A., AND TAYLOR, A. E.: Histamine's effect on pulmonary vascular resistance and compliance at elevated tone. Am. J. Physiol. **257:** H618–H625, 1989.

BARNES, P. J.: Neural control of human airways in health and disease. Am. Rev. Respir. Dis. **134:** 1289–1314, 1986.

BARNES, P. J.: Endothelins and pulmonary disease. J. Appl. Physiol. **77:** 1051–1059, 1994.

BARNES, P. J., BARANIUK, J., AND BELVISI, M. G.: Neuropeptides in the respi-

ratory tract. Am. Rev. Respir. Dis. **144:** 1187–1198, 1391–1399, 1991.
BARNES, P. J., CADIEUX, A., CARSTAIRS, J. R., GREENBERG, B., POLAK, J. M., AND RHODEN, K.: Vasoactive intestinal peptide in bovine pulmonary artery: localisation, function and receptor autoradiography. Br. J. Pharmacol. **89:** 157–162, 1986.
BARNARD, J. W., WILSON, P. S., MOORE, T. M., THOMPSON, J. W., AND TAYLOR, A. E.: Effect of nitric oxide and cyclooxygenase products on vascular resistance in dog and rat lungs. J. Appl. Physiol. **74:** 2940–2948, 1993.
BARST, R. J.: Pharmacologically induced pulmonary vasodilatation in children and young adults with primary pulmonary hypertension. Chest **89:** 497–503, 1986.
BARTSCH, P., SHAW, S., FRANCIOLLI, M., GNADINGER, M. P., AND WEIDMANN, P.: Atrial natriuretic peptide in acute mountain sickness. J. Appl. Physiol. **65:** 1929–1937, 1988.
BATRA, A. K., SEGALL, P. H., AND AHMED, T.: Pulmonary edema with nifedipine in primary pulmonary hypertension. Respiration **47:** 161–163, 1985.
BELLAN, J. A., MINKES, R. K., HOOD, J. S., MCMAHON, T. J., HIGUERA, T. R., NOSSAMAN, B. D., MCNAMARA, D. B., AND KADOWITZ, P. J.: Analysis of pulmonary and systemic vascular responses to platelet-activating factor in the cat. Am. J. Physiol. **263:** H234–H243, 1992.
BELTRAN GAMEZ, M. E., SANDOVAL ZARATE, J., SEOANE, M., AND LUPI-HERRERA, E.: Ten years' experience in the use of vasodilator agents in the treatment of primary pulmonary arterial hypertension (P-PAH) (1977–1987). Arch. Inst. Cardiol. Mex. **58:** 281–291, 1988.
BENUMOF, J. L., FUKUNAGA, A. F., AND TROUSDALE, F. R.: ATP inhibits hypoxic pulmonary vasoconstriction. (abstract) Anesthesiology **57:** A474, 1982.
BENUMOF, J. L. AND WAHRENBROCK, E. A.: Blunted hypoxic pulmonary vasoconstriction by increased lung vascular pressures. J. Appl. Physiol. **38:** 846–850, 1975.
BERKOV, S.: Hypoxic pulmonary vasoconstriction in the rat. The necessary role of angiotensin II. Circ. Res. **35:** 256–261, 1974.
BERNER, M., BEGHETTI, M., RICOU, B., ROUGE, J. C., PRETRE, R., AND FRIEDLI, B.: Relief of severe pulmonary hypertension after closure of a large ventricular septal defect using low dose inhaled nitric oxide. Intensive Care Med. **9:** 75–77, 1993.
BERRIDGE, M. J. AND IRVINE, R. F.: Inositol phosphates and cell signalling. Nature (Lond.) **341:** 197–205, 1989.
BIAGGIONI, I., KING, L. S., ENAYAT, N., ROBERTSON, D., AND NEWMAN, J. H.: Adenosine produces pulmonary vasoconstriction in sheep. Evidence for thromboxane A2/prostaglandin endoperoxide-receptor activation. Circ. Res. **65:** 1516–1525, 1989.
BIRNBAUMER, L.: G protein in signal transduction. Annu. Rev. Pharmacol. Toxicol. **30:** 675–705, 1990.
BISHOP, J. M.: The circulatory effects of bradykinin in normal subjects and patients with chronic bronchitis. Br. J. Pharmacol. **25:** 456–459, 1965.
BLOCH, K. D., EDDY, R. L., SHOWS, T. B., AND QUERTERMOUS, T.: cDNA cloning and chromosomal assignment of the gene encoding endothelin-3. J. Biol. Chem. **264:** 18156–18161, 1989.
BLOMQVIST, H., WICKERTS, C. J., ANDREEN, M., ULLBERG, U., ORTQVIST, A., AND FROSTELL, C.: Enhanced pneumonia resolution by inhalation of nitric oxide. Acta Anaesthesiol. Scand. **37:** 110–114, 1993.
BOE, J., AND SIMONSSON, B. G.: Adrenergic receptors and sympathetic agents in isolated human pulmonary arteries. Eur. J. Respir. Dis. **61:** 195–202, 1980.
BOE, J., AND SIMONSSON, B. G.: Effects of angiotensin II and bradykinin on isolated human pulmonary arteries. Eur. J. Respir. Dis. **62:** 95–101, 1981.
BOLOTINA, V. M., NAJIBI, S., PALACINO, J. J., PAGANO, P. J., AND COHEN, R. A.: Nitric oxide directly activates calcium-dependent potassium channels in vascular smooth muscle. Nature (Lond.) **368:** 850–853, 1994.
BOLTON, T. B., AND CLAPP, L. H.: Endothelial-dependent relaxant actions of carbachol and substance P in arterial smooth muscle. Br. J. Pharmacol. **87:** 713–723, 1986.
BOWMAN, A., AND MCGRATH, J. C.: The effect of hypoxia on neuroeffector transmission in the bovine retractor penis and rat anococcygeus muscles. Br. J. Pharmacol. **85:** 869–875, 1085.
BRADLEY, D. E., MCNARY, W. F., AND E. L.-BERMANI, A. W.: The distribution of acetylcholinesterase and catecholamine containing nerves in the rat lung. Anat. Rec. **167:** 205–207, 1970.
BRAIN, S. D., AND WILLIAMS, T. J.: Inflammatory oedema induced by synergism between calcitonin gene-related peptide (CGRP) and mediators of increased vascular permeability. Br. J. Pharmacol. **86:** 855–860, 1985.
BRASHERS, V. L., PEACH, M. J., AND ROSE, C. E. J.: Augmentation of hypoxic pulmonary vasoconstriction in the isolated perfused rat lung by in vitro antagonists of endothelium-dependent relaxation. J. Clin. Invest. **82:** 1495–1502, 1988.
BROWNLEE, J. R., BEEKMAN, R. H., AND ROSENTHAL, A.: Acute hemodynamic effects of nifedipine in infants with bronchopulmonary dysplasia and pulmonary hypertension. Pediatr. Res. **24:** 186–190, 1988.
BRUNNER, F., AND KUKOVETZ, W. R.: Radioligand binding to muscarinic receptors of bovine aortic endothelial cells. Br. J. Pharmacol. **102:** 373–380, 1991.
BRUNNER, F., KUHBERGER, E., GROSCHNER, K., POCH, G., AND KUKOVETZ, W. R.: Characterization of muscarinic receptors mediating endothelium-dependent relaxation of bovine coronary artery. Eur. J. Pharmacol. **200:** 25–33, 1991.
BUGA, G. M., AND IGNARRO, L. J.: Electrical field stimulation causes endothelium-dependent and nitric oxide-mediated relaxation of pulmonary artery. Am. J. Physiol. **262:** H973–H979, 1992.
BURGHUBER, O., MATHIAS, M. M., MCMURTRY, I. F., REEVES, J. T., AND VOELKEL, N. F.: Lung edema due to hydrogen peroxide is independent of cyclooxygenase products. J. Appl. Physiol. **56:** 900–905, 1984.
BURGHUBER, O. C.: Nifedipine attenuates acute hypoxic pulmonary vasoconstriction in patients with chronic obstructive pulmonary disease. Respiration **52:** 86–93, 1987.
BURHOP, K. E., VAN DER ZEE, H., BIZIOS, R., KAPLAN, J. E., AND MALIK, A. B.: Pulmonary vascular response to platelet-activating factor in awake sheep and the role of cyclooxygenase metabolites. Am. Rev. Respir. Dis. **134:** 548–554, 1986.
BURNSTOCK, G., AND KENNEDY, C.: Is there a basis for distinguishing two types of P_2-purinoceptor? Gen. Pharmacol. **16:** 433–440, 1985.
BUSH, A., BUSST, C., BOOTH, K., KNIGHT, W. B., AND SHINEBOURNE, E. A.: Does prostacyclin enhance the selective pulmonary vasodilator effect of oxygen in children with congenital heart disease? Circulation **74:** 135–144, 1986.
BUSH, A., BUSST, C. M., KNIGHT, W. B., AND SHINEBOURNE, E. A.: Comparison of the haemodynamic effects of epoprostenol (prostacyclin) and tolazoline. Br. Heart J. **60:** 141–148, 1988.
BUSH, A., BUSST, C. M., AND SHINEBOURNE, E. A.: The use of oxygen and prostacyclin as pulmonary vasodilators in congenital heart disease. Intern. J. Cardiol. **9:** 267–274, 1985.
BUZZARD, C. J., PFISTER, S. L., AND CAMPBELL, W. B.: Endothelium-dependent contraction in rabbit pulmonary artery are mediated by thromboxane A_2. Circ. Res. **72:** 1023–1034, 1993.
CAPLAN, M. S., HSUEH, W., SUN, X-M., GIDDING, S. S., AND HAGEMAR, J. R.: Circulating plasma platelet activating factor in persistent pulmonary hypertension of the newborn. Am. Rev. Respir. Dis. **142:** 1258–1262, 1990.
CARSTAIRS, J. R., AND BARNES, P. J.: Visualization of vasoactive intestinal peptide receptors in human and guinea pig lung. J. Pharmacol. Exp. Ther. **239:** 249–255, 1986a.
CARSTAIRS, J. R., AND BARNES, P. J.: Autoradiographic mapping of substance P receptors in lung. Eur. J. Pharmacol. **127:** 295–296, 1986b.
CARSTAIRS, J. R., NIMMO, A. J., AND BARNES, P. J.: Autoradiographic visualization of beta-adrenoceptor subtypes in human lung. Am. Rev. Respir. Dis. **132:** 541–547, 1985.
CASSIN, S., DAWES, G. S., MOTT, J. C., ROSS, B. B., AND STRANG, L. B.: The vascular resistance of the foetal and newly ventilated lung of the lamb. J. Physiol. (Lond.) **171:** 61–79, 1964.
CASSIN, S., TOD, M., PHILIPS, J., FRISINGER, J., JORDAN, J., AND GIBBS, C.: Effects of prostaglandin D_2 on perinatal circulation. Am. J. Physiol. **240:** H755–H760, 1981a.
CASSIN, S., WINIKOR, I., TOD, M., PHILIPS, J., FRISINGER, J., JORDAN, J., AND GIBBS, C.: Effects of prostacyclin on the fetal pulmonary circulation. Pediatr. Pharmacol. **1:** 197–207, 1981b.
CATRAVAS, J. D., BUCCAFUSCO, J. J., AND E. L. KASHEF, H.: Effects of acetylcholine in the pulmonary circulation of rabbits. J. Pharmacol. Exp. Ther. **231:** 236–241, 1984.
CECH, S.: Adrenergic innervation of blood vessels in the lung of some mammals. Acta Anat. **74:** 169–182, 1969.
CECH, S.: Cholinesterase-containing nerve fibres on blood vessels in lungs of some laboratory mammals. Z. Zellforsch. Mikrosk. Anat. **140:** 91–100, 1973.
CECH, S., AND DOLEZEL, S.: Monoaminergic innervation of the pulmonary vessels in various laboratory animals (rat, rabbit, cat). Experientia (Basel) **23:** 114–115, 1967.
CEDERQVIST, B., WIKLUND, N. P., PERSSON, M. G., AND GUSTAFSSON, L. E.: Modulation of neuroeffector transmission in the guinea pig pulmonary artery by endogenous nitric oxide. Neurosci. Lett. **127:** 67–69, 1991.
CELERMAJER, D. S., CULLEN, S., AND DEANFIELD, J. E.: Impairment of endothelium-dependent pulmonary artery relaxation in children with congenital heart disease and abnormal pulmonary hemodynamics. Circulation **87:** 440–446, 1993.
CELERMAJER, D. S., DOLLERY, C., BURCH, M., AND DEANFIELD, J. E.: Role of endothelium in the maintenance of low pulmonary vascular tone in normal children. Circulation **89:** 2041–2044, 1994.
CERDA, E., ESTEBAN, A., DE LA CAL, M. A., FERNANDEZ, A., AND GARCIA, A.: Hemodynamic effects of vasodilators on pulmonary hypertension in decompensated chronic obstructive pulmonary disease. Crit. Care Med. **13:** 221–223, 1985.
CHAND, N., AND ALTURA, B. M.: Reactivity and contractility of rat main pulmonary artery to vasoactive agents. J. Appl. Physiol. **49:** 1016–1021, 1980.
CHAND, N., AND ALTURA, B. M.: Acetylcholine and bradykinin relax intrapulmonary arteries by acting on endothelial cells: role in lung vascular diseases. Science (Wash., DC) **213:** 1376–1379, 1981.
CHANG, J-K., MOORE, P., FINEMAN, J. R., SOIFER, S. J., AND HEYMANN, M. A.: K^+ channel pulmonary vasodilation in fetal lambs: role of endothelium-derived nitric oxide. J. Appl. Physiol. **73:** 188–194, 1992.
CHEN, G., SUZUKI, H., AND WESTON, A. H.: Acetylcholine releases endothelium-derived hyperpolarizing factor and EDRF fron rat blood vessels. Br. J. Pharmacol. **95:** 1165–1174, 1988.
CHEN, C-R., VOELKEL, N. F., AND CHANG, S-W.: Pulmonary vascular reactivity: effect of PAF and PAF antagonists. J. Appl. Physiol. **73:** 1762–1769, 1992.
CHEN, C-R., VOELKEL, N. F., AND CHANG, S-W.: Platelet-activating factor

potentiates protamine-induced lung edema. Am. J. Respir. Crit. Care Med. **149:** 34–40, 1994.
CHERRY, P. D., FURCHGOTT, R. F., ZAWADZKI, J. D., AND JOTHIANANDAN, D.: The role of endothelial cells in the relaxation of isolated arteries by bradykinin. Proc. Natl. Acad. Sci. USA **79:** 2105–2110, 1982.
CHERRY, P. D., AND GILLIS, C. N.: Evidence for the role of endothelium-derived relaxing factor in acetylcholine-induced vasodilatation in the intact lung. J. Pharmacol. Exp. Ther. **241:** 516–520, 1987.
CIGARINI, I., ADNOT, S., CHABRIER, P. E., VIOSSAT, I., BRAQUET, P., AND GAUJOUR, B.: Pulmonary vasodilator responses to atrial natriuretic factor and sodium nitroprusside. J. Appl. Physiol. **67:** 2269–2275, 1989.
CLAPP, L. H., DAVEY, R., AND GURNEY, A. M.: ATP-sensitive K^+ channels mediate vasodilation produced by lemakalim in rabbit pulmonary artery. Am. J. Physiol. **264:** H1907-H1915, 1993.
CLAPP, L. H., AND GURNEY, A. M.: ATP-sensitive K^+ channels regulate resting potential of pulmonary arterial smooth muscle cells. Am. J. Physiol. **262:** H916–H920, 1992.
CLARKE, C.: Prostacyclin infusion in ARDS. Anesthesiology **73:** 194–195, 1990.
CLOUGHERTY, P. W., NYHAN, D. P., CHEN, B. B., GOLL, H. M., AND MURRAY, A. P.: Autonomic nervous system pulmonary vasoregulation after hypoperfusion in conscious dogs. Am. J. Physiol. **254:** H976-H983, 1988.
CLOZEL, M., BREU, V., BURRI, K., CASSAL, J-M., FISCHLI, W., GRAY, G. A., HIRTH, G., LOFFLER, M., MULLER, M., NEIDHART, W., AND RAMUZ, H.: Pathophysiological role of endothelin revealed by the first orally active endothelin receptor antagonist. Nature (Lond.) **365:** 759–761, 1993.
COCKS, T. M. AND ANGUS, J. A.: Endothelium-dependent relaxation of coronary arteries by noradrenaline and serotonin. Nature (Lond.) **305:** 627–630, 1983.
COCKS, T. M. AND ARNOLD, P. J.: 5-hydroxytryptamine (5-HT) mediates potent relaxation in the sheep isolated pulmonary vein via activation of 5-HT_4 receptors. Br. J. Pharmacol. **107:** 591–596, 1992.
COLEBATCH, H. J. H., DAWES, G. S., GOODWIN, J. W., AND NADEAU, R. A.: Vasodilation in the foetal and new-born lung. J. Physiol. (Lond.) **176:** 10P, 1965.
COLEBATCH, H. J. H., AND HALMAGYI, D. F. J.: Effect of vagotomy and vagal stimulation on lung mechanics and circulation. J. Appl. Physiol. **18:** 871–878, 1963.
COLICE, G. L., MATTHAY, M. A., BASS, E., AND MATTHAY, R. A.: Neyrogenic pulmonary edema. Am. Rev. Respir. Dis. **130:** 941–948, 1984.
COLLIS, M. G., AND HOURANI, S. M. O.: Adenosine receptor subtypes. Trends Pharmacol. Sci. **14:** 360–366, 1993.
COMROE, J. H. J., LINGEN, B. V., STROUD, G. C., AND RONCORNI, A.: Reflex and direct cardiopulmonary effects of 5-OH-tryptamine (serotonin). The possible role in pulmonary embolism and coronary thrombosis. Am. J. Physiol. **73:** 379–386, 1953.
CONRAADS, V. M., BOSMANS, J. M., VRINTS, C. J., CLAEYS, M. J., AND SNOECK, J. P.: Acetylcholine induces a paradoxic increase of pulmonary vascular resistance in patients with primary pulmonary hypertension. (abstract) Endothelium **1** (Suppl.): S86, 1993.
CONRAD, K. E., JOFFE, G. M., KRUSZYNA, H., KRUSZYNA, R., ROCHELLE, L. G., SMITH, R. G, CHAVEZ, J. E., AND MOSHER, M. D.: Identification of increased nitric oxide biosynthesis during pregnancy in rats. FASEB J. **7:** 566–571, 1993.
COOKE, J. P., ROSSITCH, E., JR., ANDON, N. A., LOSCALZO, J., AND DZAU, V. J.: Flow activates an endothelial potassium channel to release an endogenous nitrovasodilator. J. Clin. Invest. **88:** 1663–1671, 1991.
CORNFIELD, D. N., CHATFIELD, B. A., MCQUESTON, J. A., MCMURTRY, I. F., AND ABMAN, S. H.: Effects of birth-related stimuli on L-arginine-dependent pulmonary vasodilation in ovine fetus. Am. J. Physiol. **262:** H1474–H1481, 1992.
CORNFIELD, D. N., STEVENS, T., MCMURTRY, I. F., ABMAN, S. H., AND RODMAN, D. M.: Acute hypoxia causes membrane depolarization and calcium influx in fetal pulmonary artery smooth muscle cells. Am. J. Physiol. **266:** L469–L475, 1994.
CORRIVEAU, M. L., VU-DINH MINH, AND DOLAN, G. F.: Long-term effects of hydralazine on ventilation and blood gas values in patients with chronic obstructive pulmonary disease and pulmonary hypertension. Am. J. Med. **83:** 886–892, 1987.
CORTE, P., AND YOUNG, I. H.: Ventilation-perfusion relationships in symptomatic asthma. Response to oxygen and clemastine. Chest **88:** 167–175, 1985.
COSTA, M., AND MAJEWSKI, H.: Facilitation of noradrenaline release from sympathetic nerves through activation of ACTH receptors, beta-adrenoceptors and angiotensin II receptors. Br. J. Pharmacol. **95:** 993-1001, 1988.
CRAWLEY, D. E., LIU, S. F., BARNES, P. J., AND EVANS, T. W.: Endothelin-3 is a potent pulmonary vasodilator in the rat. J. Appl. Physiol. **72:** 1425–1431, 1992a.
CRAWLEY, D. E., LIU, S. F., EVANS, T. W., AND BARNES, P. J.: Inhibitory role of endothelium-derived nitric oxide in rat and human pulmonary arteries. Br. J. Pharmacol. **101:** 166–170, 1990.
CRAWLEY, D. E., LIU, S. F., EVANS, T. W., YACOUB, M., AND BARNES, P. J.: Role of potassium channels in relaxations of human small pulmonary arteries (abstract). Am. Rev. Respir. Dis. **145:** A228, 1992b.
CRAWLEY, D. E., ZHAO, L., GIEMBYCZ, M. A., LIU, S., BARNES, P. J., WINTER, R. J., AND EVANS, T. W.: Chronic hypoxia impairs soluble guanylyl cyclase-mediated pulmonary arterial relaxation in the rat. Am. J. Physiol. **263:** L325–L332, 1992c.
CROWELL, R. E., VAN EPPS, D. E., AND REED, W. P.: Response of isolated pulmnoary arteries to to synthetic peptide f-Met-Leu-Phe. Am. J. Physiol. **260:** H107–H112, 1989.
D'ORLEANS-JUSTE, P., DION, S., AND REGOLI, D.: Different receptors are involved in the endothelium-dependent relaxation and the smooth muscle contraction of rabbit pulmonary artery in response to substance P and related neurokinins. Eur. J. Pharmacol. **125:** 37–44, 1986.
DAL NOGARE, A. R., AND RUBIN, L. J.: The effects of hydralazine on exercise capacity in pulmonary hypertension secondary to chronic obstructive pulmonary disease. Am. Rev. Respir. Dis. **133:** 385–389, 1986.
DALY, I., AND DALY, M.: Proceedings: Sympathetic nerve control of pulmonary vascular resistance and impedance in isolated perfused lungs of the dog. J. Physiol. (Lond.) **234:** 106P–108P, 1973.
DALY, I. D. B., AND DALY, M. D. B.: The effects of stimulation of the carotid body chemoreceptors on pulmonary vascular resistance in the dog. J. Physiol. (Lond.) **137:** 436–446, 1957.
DALY, I. D. B., AND DALY, M. D. B.: The effects of stimulation of the carotid body chemoreceptors on the pulmonary vascular bed in the dog: the 'vasosensory controlled perfused living animal' preparation. J. Physiol. (Lond.) **148:** 201–219, 1959.
DALY, I. D. B., AND HEBB, C.: Pulmonary vasomotor fibres in the cervical vagosympathetic nerve of dog. Q. J. Exp. Physiol. **37:** 19–43, 1952.
DALY, I. D. B., AND HEBB, C.: Innervation of of the lungs. *In* Pulmonary and Bronchial Vascular Systems, ed. by I. D. B. Daly and C. Hebb, pp. 89–117, William & Wilkins, Baltimore, 1966.
DALY, I., RAMSAY, D. J., AND WAALER, B. A.: The site of action of nerves in the pulmonary vascular bed in the dog. J. Physiol. (Lond.) **209:** 317–339, 1970.
DANTZKER, D. R., AND BOWER, J. S.: Partial reversibility of chronic pulmonary hypertension caused by pulmonary thromboembolic disease. Am. Rev. Respir. Dis. **124:** 129–131, 1981.
DAOUD, F. S., REEVES, J. T., AND SCHAEFER, J. W.: Failure of hypoxic pulmonary vasoconstriction in patients with liver cirrhosis. J. Clin. Invest. **51:** 1076–1080, 1972.
DAVAL, J-L., NEHLIG, A., AND NICOLAS, F.: Physiological and pharmacological properties of adenosine: therapeutic implications. Life Sci. **49:** 1435–1453, 1991.
DAVIDSON, D.: Circulating vasoactive substances and hemodynamic adjustments at birth in lambs. J. Appl. Physiol. **63:** 676–684, 1987.
DAVIDSON, D., AND DRAFTA, D.: Prolonged pulmonary hypertension caused by platelet-activating factor and leukotriene C_4 in the rat lung. J. Appl. Physiol. **73:** 955–961, 1992.
DAVIDSON, D., AND ELDEMERDASH, A.: Endothelium-derived relaxing factor: presence in pulmonary and systemic arteries of the newborn guinea pig. Pediatr. Res. **27:** 128–132, 1990.
DAVIDSON, D., AND ELDEMERDASH, A.: Endothelium-derived relaxing factor: evidence that it regulates pulmonary vascular resistance in the isolated neonatal guinea pig lung. Pediatr. Res. **29:** 538–542, 1991.
DAWSON, C. A., GRIMM, D. J., AND LINEHAN, J. H.: Lung inflation and longitudinal distribution of pulmonary vascular resistance during hypoxia. J. Appl. Physiol. **47:** 532–536, 1979.
DE MEY, J. G., AND VANHOUTTE, P. M.: Heterogeneous behavior of the canine arterial and venous wall. Importance of the endothelium. Circ. Res. **51:** 439–447, 1982.
DE MICHELE, M., CAVALLOTTI, C., AND AMENTA, F.: Autoradiographic localization of muscarinic acetylcholine receptors in the rat pulmonary vascular tree. Eur. J. Pharmacol. **192:** 71–78, 1991.
DEMIRYUREK, A. T., WADSWORTH, R. M., AND KANE, K. A.: Effects of hypoxia on isolated intrapulmonary arteries from the sheep. Pulm. Pharmacol. **4:** 158–164, 1991.
DEY, R. D., AND SAID, S. I.: Lung peptides and pulmonary circulation. *In* The Pulmonary Circulation and Acute Lung Injury, ed. by S. I. Said, pp. 101–122, Futura Publishing Co., New York, 1985.
DEY, R. D., SHANNON, W. A., JR., AND SAID, S. I.: Localization of VIP-immunoreactive nerves in airways and pulmonary vessels of dogs, cat, and human subjects. Cell Tissue Res. **220:** 231–238, 1981.
DIETERLE, Y., ODY, C., EHRENSBERGER, A., STALDER, H., AND JUNOD, A. F.: Metabolism and uptake of adenosine triphosphate and adenosine by porcine aortic and pulmonary endothelial cells and fibroblasts in culture. Circ. Res. **42:** 869–876, 1978.
DINH-XUAN, A. T.: Disorders of endothelium-dependent relaxation in pulmonary disease. Circulation **87** (Suppl. V): V-81–V-87, 1993.
DINH-XUAN, A. T., HIGENBOTTAM, T. W., CLELLAND, C. A., PEPKE-ZABA, J., CREMONA, G., BUTT, A. Y., LARGE, S. R., WELLS, F. C., AND WALLWORK, J.: Impairment of endothelium-dependent pulmonary-artery relaxation in chronic obstructive lung disease. N. Engl. J. Med. **324:** 1539–1547, 1991.
DINH-XUAN, A. T., HIGENBOTTAM, T. W., CLELLAND, C., PEPKE-ZABA, J., CREMONA, G., AND WALLWORK, J.: Impairment of endothelium-dependent relaxation in patients with Eisenmenger's syndrome. Br. J. Pharmacol. **99:** 9–10, 1990.
DOCHERTY, J. R., AND STARKE, K.: Postsynaptic alpha-adrenoceptor subtypes in rabbit blood vessels and rat anococcygeus muscle studied in vitro. J. Cardiovasc. Pharmacol. **3:** 854–866, 1981.
DRUML, W., STELTZER, H., WALDHAUSL, W., LENZ, K., HAMMERLE, A., VIERHAP-

PER, H., GASIC, S., AND WAGNER, O. F.: Endothelin-1 in adult respiratory distress syndrome. Am. Rev. Respir. Dis. **148:** 169–173, 1993.
DUKE, H. N.: The site of action of anoxia on the pulmonary blood vessels of the cat. J. Physiol. (Lond.) **125:** 373–382, 1954.
DUKE, H. N., AND STEDEFORD, R. D.: Pulmonary vasomotor responses to epinephrine and norepinephrine in the cat. Influence of sympathetic nervous system. Circ. Res. **8:** 640, 1960.
DUPUY, P. M., SHORE, S. A., DRAZEN, J. M., FROSTELL, C., HILL, W. A., AND ZAPOL, W. M.: Bronchodilator action of inhaled nitric oxide in guinea pigs. J. Clin. Invest. **90:** 421–428, 1992.
EDDAHIBI, S., RAFFESTIN, B., BRAQUET, P., CHABRIER, P. E., AND ADNOT, S.: Pulmonary vascular reactivity to endothelin-1 in normal and chronic pulmonary hypertensive rats. J. Cardiovasc. Pharmacol. **17** (Suppl)**:** 358–362, 1991.
EL-BERMANI, A-W. I.: Pulmonary nonadrenergic innervation of rat and monkey. Thorax **33:** 167–174, 1978.
EL-KASHEF, H., AND CATRAVAS, J. D.: The nature of muscarinic receptor subtypes mediating pulmonary vasoconstriction in the rabbit. Pulm. Pharmacol. **4:** 8–19, 1991.
EL-KASHEF, H. A., HOFMAN, W. F., EHRHART, I. C., AND CATRAVAS, J. D.: Multiple muscarinic receptor subtypes in the canine pulmonary circulation. J. Appl. Physiol. **71:** 2032–2043, 1991.
ELTON, T. S., OPARIL, S., TAYLOR, G. R., HICKS, P. H., YANG, R-H., JIN, H., AND CHEN, Y. F.: Normobaric hypoxia stimulates endothelin-1 gene expression in the rat. Am. J. Physiol. **263:** R1260–R1264, 1992.
EMERY, C. J., BEE, D., AND BARER, G. R.: Mechanical properties and reactivity of vessels in isolated perfused lungs of chronically hypoxic rats. Clin. Sci. **61:** 569–580, 1981.
ERDÖS, E. G., JOHNSON, A. R., AND BOYDEN, N. T.: Hydrolysis of enkephalin by cultured human endothelial cells and by purified peptidyl dipeptidase. Biochem. Pharmacol. **27:** 843–848, 1978.
ERLING, D., YOO, H., EDVINSSON, L., REIS, D. J., AND WAHLESTEDT, C.: Mitogenic effects of ATP on vascular smooth muscle cells vs. other growth factors and sympathetic cotransmitters. Am. J. Physiol. **265:** H1089–H1097, 1993.
ESMORE, D. S., SPRATT, P. M., BRANCH, J. M., KEOGH, A. M., LEE, R. P., FARNSWORTH, A. E., SHANAHAN, M. X., AND CHANG, V. P.: Right ventricular assist and prostacyclin infusion for allograft failure in the presence of high pulmonary vascular resistance. J. Heart Transplant. **9:** 136–141, 1990.
ESTERLY, J. A., GLAGOV, S., AND FERGUSON, D. J.: Morphogenesis of intimal obliterative hyperplasia of small arteries in experimental pulmonary hypertension. Am. J. Pathol. **52:** 325–337, 1968.
ETHIER, M. F., CHANDER, V., AND DOBSON, JR., J. G.: Adenosine stimulates proliferation of human endothelial cells in culture. Am. J. Physiol. **265:** H131–H138, 1993.
FAN, M., WANG, D. X., AND ZHU, Z. H.: Alteration in hypoxic pulmonary vasoconstriction during hypothermia in dogs. J. Tongji Med. Univ. **2:** 134–138, 1992.
FILLENZ, M.: Innervation of pulmonary and bronchial blood vessels of the dog. J. Anat. **106:** 449–461, 1970.
FINEMAN, J. R., CHANG, R., AND SOIFER, S.: L-arginine, a precursor of EDRF in vitro, produces pulmonary vasodilation in the lambs. Am. J. Physiol. **261:** H1563–H1569, 1991b.
FINEMAN, J. R., HEYMANN, M. A., AND SOIFER, S. J.: N-omega-nitro-L-arginine attenuates endothelium-dependent pulmonary vasodilation in lambs. Am. J. Physiol. **260:** H1299–H1306, 1991a.
FISHER, J., BORER, J. S., MOSES, J. W., GOLDBERG, H. L., NIARCHOS, A. P., WHITMAN, H. H., AND MERMELSTEIN, M.: Hemodynamic effects of nifedioine versus hydralazine in primary pulmonary hypertension. Am. J. Cardiol. **54:** 646–650, 1984.
FISHMAN, A. P.: Respiratory gases in the regulation of the pulmonary circulation. Physiol. Rev. **41:** 214–280, 1961.
FISHMAN, A. P.: Hypoxia on the pulmonary circulation. How and where it acts. Circ. Res. **38:** 221–231, 1976.
FITZGERALD, R. S., DEHGHANI, G. A., SHAM, D. J., SHIRAHATA, M., AND MITZNER, W. A.: Peripheral chemoreceptor modulation of the pulmonary vasculature in the cat. J. Appl. Physiol. **73:** 20–29, 1992.
FRANCOIS-FRANCK, C. A.: Étude critique et experimentale de la vasoconstistion pulmonaire reflexe. Arch. Physiol. Norm. Pathol. **18:** 193–198, 1896.
FRANGOS, J. A., ESKIN, S. G., MCINTIRE, L. V., AND IVES, C. L.: Flow effects on prostacyclin production by cultured human endothelial cells. Science (Wash. DC) **227:** 1477–1479, 1985.
FRANK, G. W., AND BEVAN, J. A.: Electrical stimulation causes endothelium-dependent relaxation in lung vessels. Am. J. Physiol. **244:** H793–H798, 1983.
FRANTZ, E., SOIFER, S. J., CLYMAN, R. I., AND HEYMANN, M. A.: Bradykinin produces pulmonary vasodilation in fetal lambs: role of prostaglandin production. J. Appl. Physiol. **67:** 1512–1517, 1989.
FRIEDMAN, L. S., FITZPATRICK, T. M., BLOOM, M. F., RAMWELL, P. W., ROSE, J. C., AND KOT, P. A.: Cardiovascular and pulmonary effects of thromboxane B_2 in the dog. Circ. Res. **44:** 748–751, 1979.
FRITTS, J., HARRIS, P., CLAUSS, R. H., ODELL, J. E., AND COURNAND, A.: The effect of acetylcholine on the human pulmonary circulation under normal and hypoxic conditions. J. Clin. Invest. **37:** 99–110, 1958.
FROSTELL, C., FRATACCI, M-D., WAIN, J. C., JONES, R., AND ZAPOL, W. M.: Inhaled nitric oxide. A selective pulmonary vasodilator reverses hypoxic pulmonary vasoconstriction. Circulation **83:** 2038–2047, 1991.
FU, J-Y., MASFERRER, J. L., SEIBERT, K., RAZ, A., AND NEEDLEMAN, P.: The induction and suppression of prostaglandin H_2 synthase (cylooxygenase) in human monocytes. J. Biol. Chem. **265:** 16737–16740, 1990.
FUJIMOTO, K., SAKAI, A., YOSHIKAWA, S., SHINOZAKI, S., MATSUZAWA, Y., KUBO, K., KOBAYASHI, T., UEDA, G., SEKIGUCHI, M., AND VOELKEL, N. F.: Effect of cyclic guanosine monophosphate on hypoxic and angiotensin-II-induced pulmonary vasoconstriction. Lung **168:** 333–343, 1990.
FURCHGOTT, R. F.: The role of endothelium in the responses of vascular smooth muscle to drugs. Annu. Rev. Pharmacol. Toxicol. **24:** 175–197, 1984.
FURCHGOTT, R. F.: Studies on relaxation of rabbit aorta by sodium nitrite: the basis for the proposal that acid-activable inhibitory factor from bovine retrator penis is inorganic nitrite and the endothelium-derived relaxing factor is nitric oxide. *In* Vasodilatation: Vascular Smooth Muscle, Peptides, Autonomic Nerves and Endothelium, ed. by P. M. Vanhoutte, pp. 401–414, Raven Press, New York, 1988.
FURCHGOTT, R. F., AND VANHOUTTE, P. M.: Endothelium-derived relaxing and contracting factors. FASEB J. **3:** 2007–2018, 1989.
FURCHGOTT, R. F., AND ZAWADZKI, J. V.: The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. Nature (Lond.) **288:** 373–376, 1980.
FURNESS, J. B., PAPKA, R. E., DELLA, N. G., COSTA, M., AND ESKAY, R. L.: Substance P-like immunoreactivity in nerves associated with the vascular system of guinea-pigs. Neuroscience **7:** 447–459, 1982.
GABA, S. J., BOURGOUIN-KARAOUNI, D., DUJOLS, P., MICHEL, F. B., AND PREFAUT, C.: Effects of adenosine triphosphate on pulmonary circulation in chronic obstructive pulmonary disease. ATP: a pulmonary vasoregulator? Am. Rev. Respir. Dis. **134:** 1140–1144, 1986.
GALIE, N., SANGUINETTI, M., MARROZZINI, C., AND MAGNANI, B.: Vasodilator therapy in chronic thromboembolic cor pulmonare. Description of a case with unfavorable hemodynamic effects. G. Ital. Cardiol. **15:** 992–994, 1985.
GARCIA-SZABO, R. R., PETERSON, M. B., WATKINS, W. D., BIZIOS, R., KONG, D. L., AND MALIK, A. B.: Thromboxane generation after thrombin. Protective effect of thromboxane synthetase inhibition on lung fluid balance. Circ. Res. **53:** 214–222, 1983.
GARDINER, S. M., RAKHIT, T., KEMP, P. A., MARCH, J. E., AND BENNETT, T.: Regional haemodynamic response to pituitary adenylate cyclase-activating polypeptide and vasoactive intestinal polypeptide in conscious rats. Br. J. Pharmacol. **111:** 589–597, 1994.
GARG, U. C., AND HASSID, A.: Nitric oxide-generating vasodilators and 8-bromo-cyclic guanosine monophosphate inhibit mitogenesis and proliferation of cultured rat vascular smooth muscle cells. J. Clin. Invest. **83:** 1774–1777, 1989.
GASSNER, A., FRIDRICH, L., MAGOMETSCHNIGG, D., SOMMER, G., AND KLICPERA, M.: Vasodilator therapy in pulmonary hypertension and chronic obstructive lung disease (COPD). Hemodynamic studies exemplified by nifedipine and nitroglycerin. Herz **11:** 207–216, 1986.
GASSNER, A., SOMMER, G., FRIDRICH, L., MAGOMETSCHNIGG, D., AND PRIOL, A.: Differential therapy with calcium antagonists in pulmonary hypertension secondary to COPD. Hemodynamic effects of nifedipine, diltiazem, and verapamil. Chest **98:** 829–834, 1990.
GERAADS, A., LEVY, P., BRAMBILLA, C., AND PARAMELLE, B.: Desaturation and nocturnal pulmonary arterial hypertension in C.O.P.D.: effects of oxygen therapy. Rev. Mal. Respir. **1:** 319–325, 1984.
GERBER, J. G., VOELKEL, N., NIES, A. S., MCMURTRY, I. F., AND REEVES, J. T.: Moderation of hypoxic vasoconstriction by infused arachidonic acid: role of PGI_2. J. Appl. Physiol. **49:** 107–112, 1980.
GERLACH, H., ROSSAINT, R., PAPPERT, D., AND FALKE, K.: Time course and dose-response of nitric oxide inhalation for ststemic oxygenation and pulmonary hypertension in patients with adult respiratory distress syndrome. Eur. J. Clin. Invest. **23:** 499–502, 1993.
GIAID, A., YANAGISAWA, M., LANGLEBEN, D., MICHEL, R. P., LEVY, R., SHENNIB, H., KIMURA, S., MASAKI, T., DUGUID, W. P., AND STEWART, D. J.: Expression of endothelin-1 in the lungs of patients with pulmonary hypertension. N. Engl. J. Med. **328:** 1732–1739, 1993.
GILLESPIE, M. N., OLSON, J. W., REINSEL, C. N., O'CONNOR, W. N., AND ALTIERE, R. J.: Vascular hyperresponsiveness in perfused lungs from monocrotaline-treated rats. Am. J. Physiol. **251:** H109–H114, 1986.
GILLESPIE, M. N., REINSEL, C. N., AND BOWDY, B. D.: Pulmonary vasoactivity of lung endocrine cell-related peptides. Peptides **5:** 21–24, 1984.
GIRARD, C., LEHOT, J. J., PANNETIER, J. C., FILLEY, S., FFRENCH, P., AND ESTANOVE, S.: Inhaled nitric oxide after mitral valve replacement in patients with chronic pulmonary artery hypertension. Anesthesiology **77:** 880–883, 1992.
GLAZIER, J. B., AND MURRAY, J. F.: Site of pulmonary vasomotor reactivity in the dog during alveolar hypoxia and serotonin, and histamine infusion. J. Clin. Invest. **50:** 2550–2558, 1971.
GLUSA, E., BRETSCHNEIDER, E., AND PAINTZ, M.: Contractile effects of thrombin in porcine pulmonary arteries and the influence of thrombin inhibitors. Naunyn-Schmiedeberg's Arch. Pharmacol. **349:** 101–106, 1994.
GLUSA, E. R., AND RICHTER, M.: Endothelium-dependent relaxation of porcine pulmonary arteries via 5-HT_{1c}-like receptors. Nauyn-Schmiedeberg's Arch. Pharmacol. **347:** 471–477, 1993.
GOLDERING, R. M., TURINO, G. M., JAMESON, A. G., BASS, B. G., AND FISHMAN,

A. P.: The catecholamines in the pulmonary arterial pressor response to acute hypoxia. J. Clin. Invest. **41:** 1211–1222, 1962.

GOLL, H. M., NYHAN, D. P., GELLER, H. S., AND MURRAY, P. A.: Pulmonary vascular responses to angiotensin II and captopril in conscious dogs. J. Appl. Physiol. **61:** 1552–1559, 1986.

GORDON, J. B., CLEMENT D. E., CLETY, S., AND CHU, K.: Developmental changes in vascular responses to histamine in normoxic and hypoxic lamb lungs. J. Appl. Physiol. **70:** 323–330, 1991.

GORDON, J. B., AND TOD, M. L.: Effects of N omega-nitro-L-arginine on total and segmental vascular resistances in developing lamb lungs. J. Appl. Physiol. **75:** 76–85, 1993.

GRASER, T., AND VANHOUTTE, P. M.: Hypoxic contraction of canine coronary arteries: role of endothelium and cGMP. Am. J. Physiol. **261:** H1769–H1777, 1991.

GREENBERG, S., DIECKE, F. P. J., CANTOR, E., PEEVY, K., AND TANAKA, T. P.: Inhibition of sympathetic neurotransmitter release by modulation of cyclic GMP in canine vascular smooth muscle. Eur. J. Pharmacol. **187:** 409–423, 1990.

GREENBERG, S., DIECKE, F. P. J., PEEVY, K., AND TANAKA, T. P.: Endothelium modulates adrenergic neurotransmission to canine pulmonary arteries and veins. Eur. J. Pharmacol. **162:** 67–80, 1989.

GREENBERG, B., RHODEN, K., AND BARNES, P. J.: Activated oxygen molecules generated by electrical stimulation affect vascular smooth muscle. J. Mol. Cell. Cardiol. **18:** 975–981, 1986.

GREENBERG, B., RHODEN, K., AND BARNES, P. J.: Endothelium-dependent relaxation of human pulmonary arteries. Am. J. Physiol. **252:** H434–H438, 1987a.

GREENBERG, B., RHODEN, K., AND BARNES, P. J.: Relaxant effects of vasoactive intestinal peptide and peptide histidine isoleucine in human and bovine pulmonary arteries. Blood Vessels **24:** 45–50, 1987b.

GREENBERG, S., KADOWITZ, P. J., HYMAN, A., AND CURRON, F. A.: Adrenergic mechanisms in canine intralobar pulmonary arteries and veins. Am. J. Physiol. **240:** H274–H285, 1981.

GRIFFITHS, M. J. D., MESSENT, M., MACALLISTER, J. R., AND EVANS, T. W.: Aminoguandine selectively inhibits inducible nitric oxide synthase. Br. J. Pharmacol. **110:** 963–968, 1993.

GRIGORIAN, G. I., MIRZOPOIAZOVA, T. I., NIKASHIN, A. V., GONCHAROV, N. V., AND DANILOV, S. M.: Identification and characteristics of the beta-adrenergic receptors in the membranes of cultured endothelial cells of the human pulmonary artery. Prob. Endokrinol. **35:** 37–40, 1989.

GROVES, B. M., RUBIN, L. J., FROSOLONO, M. F., CATO, A. E., AND REEVES, J. T.: A comparison of the acute hemodynamic effects of prostacyclin and hydralazine in primary pulmonary hypertension. Am. Heart J. **110:** 1200–1204, 1985.

GRUETTER, C. A., MCNAMARA, D. B., HYMAN, A. L., AND KADOWITZ, P. J.: Contractile effects of a PGH_2 analog and PGD_2 on intrapulmonary vessels. Am. J. Physiol. **234:** H139–H145, 1978.

GUADAGNI, D. N., IKRAM, H., AND MASLOWSKI, A. H.: Haemodynamic effects of prostacyclin (PGI_2) in pulmonary hypertension. Br. Heart J. **45:** 385–388, 1981.

GUAZZI, M. D., ALIMENTO, M., BERTI, M., FIORENTINI, C., GALLI, C., AND TAMBORINI, G.: Enhanced hypoxic pulmonary vasoconstriction in hypertension. Circulation **79:** 337–343, 1989.

GUTKOWSKA, J. AND NEMER, M.: Structure, expression and function of atrial natriuretic peptide in extra-atrial tissues. Endocrine Rev. **10:** 519–535, 1989.

HAKIM, T. S., DAWSON, C. A., AND LINEHAN, J. H.: Hemodynamic responses of dog lung lobe to lobar venous occlusion. J. Appl. Physiol. **47:** 145–152, 1979.

HAKIM, T. S., GRUNSTEIN, M. M., AND MICHEL, R. P.: Opiate action in the pulmonary circulation. Pulm. Pharmacol. **5:** 159–165, 1992.

HALBRUGGE, T., LUTSCH, K., THYEN, A., AND GRAEFE, K-H.: role of nitric oxide formation in the haempdynamics and the release of noradrenaline. Naunyn-Schmiedeberg's Arch. Pharmacol. **344:** 720–727, 1991.

HALES, C. A., SONNE, L., PETERSON, M., KONG, D., MILLER, M., AND WATKINS, W. D.: Role of thromboxane and prostacyclin in pulmonary vasomotor changes after endotoxin in dogs. J. Clin. Invest. **68:** 497–505, 1981.

HALES, C. A. AND WESTPHAL, D. M.: Pulmonary hypoxic vasoconstriction: not affected by chemical sympathectomy. J. Appl. Physiol. **46:** 529–533, 1979.

HAMASAKI, Y., MOJARAD, M., AND SAID, S. I.: Relaxant action of VIP on cat pulmonary artery: comparison with acetylcholine, isoproterenol, and PGE_1. J. Appl. Physiol. **54:** 1607–1611, 1983.

HAND, J. M.: Effects of leukotrienes on isolated guinea pig pulmonary arteries. Eur. J. Pharmacol. **76:** 439–442, 1981.

HANLY, P., SIENKO, A., AND LIGHT, R. B.: Effect of cyclooxygenase blockade on gas exchange and hemodynamics in *Pseudomonas* pneumonia. J. Appl. Physiol. **63:** 1829–1836, 1987.

HANNA, C. J., BACH, M. K., PARE, P. D., AND SCHELLENBERG, R. R.: Slow-reacting substances (leukotrienes) contract human airway and pulmonary vascular smooth muscle in vitro. Nature (Lond.) **290:** 343–344, 1981.

HARADA, H., ISHIZAKA, A., YONEMARU, M., MALLICK, A. A., HATHERILL, J. R., ZHENG, H., LILLY, M., O'HANLEY, P. T., AND RAFFIN, T. A.: The effects of aminophylline and pentoxifylline on multiple organ damage after Escherichia coli sepsis. Am. Rev. Respir. Dis. **140:** 947–980, 1989.

HARDER, D. R., MADDEN, J. A., AND DAWSON, C.: Hypoxic induction of Ca^{2+}-dependent action potentials in small pulmonary arteries of cat. J. Appl. Physiol. **59:** 1389–1393, 1985.

HARRIS, P., AND HEATH, D.: The Human Pulmonary Circulation, Churchill Livingstone, London, 1986.

HARRIS, P., TRITTS J. R., H., AND COURNAND, A.: Some circulatory effects of 5-hydroxytryptamine in man. Circulation **21:** 1134–1139, 1960.

HASHIBA, Y., ISHIKAWA, N., SUMITA, T., TAKAGI, K., HIDAKA, H., AND SATAKE, T.: Capsaicin-sensitive nerves exert an inhibitory effect on the development of fibrin-induced pulmonary edema in rats. Am. Rev. Respir. Dis. **140:** 652–658, 1989.

HASSESSIAN, H., BODIN, P., AND BURNSTOCK, G.: Blockade by glibenclamide of the flow-evoked endothelial release of ATP that contributes to vasodilatation in the pulmonary vascular bed of the rat. Br. J. Pharmacol. **109:** 466–472, 1993.

HASSOUN, P. M., THAPPA, V., LANDMAN, M. J., AND FANBURG, B. L.: Endothelin: mitogenic activity on pulmonary artery smooth muscle cells and release from hypoxic endothelial cells. Proc. Soc. Exp. Biol. Med. **199:** 165–170, 1992.

HASUNUMA, K., RODMAN, D. M., AND MCMURTRY, I. F.: Effects of K^+ channel blockers on vascular tone in the perfused rat lung. Am. Rev. Respir. Dis. **144:** 884–887, 1991b.

HASUNUMA, K., RODMAN, D. M., O'BRIEN, R. F., AND MCMURTRY, I. F.: Endothelin 1 causes pulmonary vasodilatation in rats. Am. J. Physiol. **259:** H48–H54, 1990.

HASUNUMA, K., YAMAGUCHI, T., RODMAN, D. M., O'BRIEN, R. F., AND MCMURTRY, I. F.: Effects of inhibitors of EDRF and EDHF on vasoreactivity of perfused rat lungs. Am. J. Physiol. **260:** L97–L104, 1991a.

HAUGE, A.: Role of histamine in hypoxic pulmonary hypertension in the rat. I. Blockade or potentiation of endogenous amines, kinins, and ATP. Circ. Res. **22:** 371–383, 1968.

HAUGE, A., LUNDE, P. K. M., AND WAALER, B. A.: The effect of bradykinin, kallidin and eledoisin upon the pulmonary vascular bed of an isolated blood-perfused rabbit lung preparation. Acta Physiol. Scand. **66:** 269, 1966.

HAUGE, A., AND MELMON, K. L.: Role of histamine in hypoxic pulmonary hypertension in the rat. II. Depletion of histamine, serotonin, and catecholamines. Circ. Res. **22:** 385–392, 1968.

HAWORTH, S. G. AND HISLOP, A. A.: Adaptation of the pulmonary circulation to extra-uterine life in the pig and its relevance to the human infant. Cardiovasc. Res. **15:** 108–119, 1981.

HAY, D. W. P., LUTTMANN, M. A., HUBBARD, W. C., AND UNDEM, B. J.: Endothelin receptor subtypes in human and guinea pig pulmonary tissues. Br. J. Pharmacol. **110:** 1175–1183, 1993.

HAYNES, J., CHANG, S. W., MORRIS, K. G., AND VOELKEL, N. F.: Platelet activating factor antagonists increase vascular reactivity in perfused rat lung. J. Appl. Physiol. **65:** 1921–1928, 1988.

HAYNES, J. J., ROBINSON, J., SAUNDERS, L., TAYLOR, A. E., AND STRADA, S. J.: Role of cAMP-dependent kinase in cAMP-mediated vasodilation. Am. J. Physiol. **262:** H511–H516, 1992.

HAYNES, W. G., AND WEBB, D. J.: The endothelin family of peptides: local hormones with diverse roles in health and disease? Clin. Sci. **84:** 485–500, 1993.

HAYWOOD, G. A., SNEDDON, J. F., BASHIR, Y., JENNISON, S. H., GRAY, H. H., AND MCKENNA, W. J.: Adenosine infusion for the reversal of pulmonary vasoconstriction in biventricular failure. Circulation **86:** 896–902, 1992.

HEBB, C.: Motor innervation of the pulmonary blood vessels of mammals. *In* The pulmonary circulation and interstitial space, ed. by A. P. Fishman and H. H. Hecht, pp. 195–222, University of Chicago Press, Chicago, 1969.

HECHTMAN, H. B., VALERI, R., AND SHEPRO, D.: Role of humoral mediators in adult respiratory distress syndrome. Chest **86:** 623–627, 1984.

HERVE, P., DROUET, L., DOSQUET, C., LAUNAY, J. M., RAIN, B., SIMONNEAU, G., CAEN, J., AND DUROUX, P.: Primary pulmonary hypertension in a patient with a familial platelet storage pool disease: role of serotonin. Am. J. Med. **89:** 117–120, 1990.

HESSLER, J. R., AND CASSIN, S.: Effects of increased intracranial pressure on pulmonary vascular resistance of fetal and neonatal goats. Am. J. Physiol. **233:** H671–H675, 1977.

HIGENBOTTAM, T., WHEELDON, D., WELLS, F., AND WALLWORK, J.: Long-term treatment of primary pulmonary hypertension with continuous intravenous epoprostenol (prostacyclin). Lancet **1:** 1046–1047, 1984.

HILL, N. S., AND OU, L. C.: The role of pulmonary vascular responses to chronic hypoxia in the development of chronic mountain sickness in rats. Respir. Physiol. **58:** 171–185, 1984.

HILL, N. S., AND ROUNDS, S.: Vascular reactivity is increased in rat lungs injured with alpha-naphthylthiourea. J. Appl. Physiol. **54:** 1693–1701, 1983.

HLA, T., AND NEILSON, K.: Human cyclooxygenase-2 cDNA. Proc. Natl. Acad. Sci. USA **89:** 7384–7388, 1992.

HOGAN, J. C., SMITH, J. A., RICHARDS, A. C., AND LEWIS, M. J.: Atrial natriuretic peptide inhibits the release of endothelium-derived relaxing factor from blood vessels of the rabbit. Eur. J. Pharmacol. **165:** 129–134, 1989.

HÖGMAN, M., FROSTELL, C. G., HEDENSTROM, H., AND HEDENSTIERNA, G.: Inhalation of nitric oxide modulates adult human bronchial tone. Am. Rev. Respir. Dis. **148:** 1474–1478, 1993.

HOOD, J. S., MCMAHON, T. J., AND KADOWITZ, P. J.: Influence of lemakalim on the pulmonary vascular bed of the cat. Eur. J. Pharmacol. **202:** 101–104, 1991a.

HOOD, J. S., MCMAHON, T. J., AND KADOWITZ, P. J.: Pulmonary vasodilator response to RP 52891 are mediated by activation of a glibenclamide-sensitive K^+_{ATP} channel. Eur. J. Pharmacol. **202:** 121–124, 1991b.
HORGAN, M. J., PINHEIRO, J. M., AND MALIK, A. B.: Mechanism of endothelin-1-induced pulmonary vasoconstriction. Circ. Res. **69:** 157–164, 1991.
HOSHINO, Y., OBARA, H., KUSUNOKI, M., FUJII, Y., AND IWAI, S.: Hypoxic contractile response in isolated human pulmonary artery: role of calcium ion. J. Appl. Physiol. **65:** 2468–2474, 1988.
HOSODA, K, NAKAO, K., AND ARAI, H.: Cloning and expression of human endothelin-1 receptor cDNA. FEBS Lett. **287:** 23–26, 1991.
HOWARD, P. G., PLUMPTON, C., AND DAVENPORT, A. P.: Anatomical localization and pharmacological activity of nature endothelins and their precursor in human vascular tissue. J. Hyperten. **10:** 1379–1386, 1992.
HU, Z-W., MILLER, J. W., AND HOFFMAN, B. B.: Induction of enhanced release of endothelium-derived relaxing factor after prolonged exposure to α-adrenergic agonist: role in desensitization of smooth muscle contraction. J. Cardiovasc. Pharmacol. **23:** 337–343, 1994.
HULME, E. C., BIRDSALL, N. J. M., AND BUCKLEY, N. J.: Muscarinic receptor subtypes. Annu. Rev. Pharmacol. **30:** 633–673, 1990.
HYMAN, A. L.: Pulmonary vasoconstriction due to nonocclusive distention of large pulmonary arteries in the dog. Circ. Res. **23:** 401–413, 1968.
HYMAN, A. L.: Neural regulation of pulmonary vascular bed. Circulation **74** (Suppl. II)**:** II-D–II-E, 1986.
HYMAN, A. L., AND KADOWITZ, P. J.: Pulmonary vasodilator activity of prostacyclin (PGI2) in the cat. Circ. Res. **45:** 404–409, 1979.
HYMAN, A. L., AND KADOWITZ, P. J.: Evidence for existence of postjunctional alpha 1- and alpha 2-adrenoceptors in cat pulmonary vascular bed. Am. J. Physiol. **249:** H891–H898, 1985.
HYMAN, A. L., AND KADOWITZ, P. J.: Tone-dependent responses to acetylcholine in the feline pulmonary vascular bed. J. Appl. Physiol. **64:** 2002–2009, 1988.
HYMAN, A. L., AND KADOWITZ, P. J.: Influence of tone on responses to acetylcholine in the rabbit pulmonary vascular bed. J. Appl. Physiol. **67:** 1388–1394, 1989.
HYMAN, A. L., KADOWITZ, P. J., AND LIPPTON, H. L.: Methylene blue selectively inhibits pulmonary vasodilator response in cats. J. Appl. Physiol. **66:** 1513–1517, 1989.
HYMAN, A. L., LIPPTON, H. L., AND KADOWITZ, P. J.: Nature of $alpha_1$ and postjunctional $alpha_2$ adrenoceptors in the pulmonary vascular bed. Fed. Proc. **45:** 2336–2340, 1986.
HYMAN, A. L., LIPPTON, H. L., AND KADOWITZ, P. J.: Analysis of pulmonary vascular responses in cats to sympathetic nerve stimulation under elevated tone conditions. Evidence that neuronally released norepinephrine acts on alpha1-, alpha2-, and beta2-adrenoceptors. Circ. Res. **67:** 862–870, 1990.
HYMAN, A. L., NANDIWADA, P., KNIGHT, D. S., AND KADOWITZ, P. J.: Pulmonary vasodilator responses to catecholamines and sympathetic nerve stimulation in the cat. Evidence that vascular beta2 adrenoreceptors are innervated. Circ. Res. **48:** 407–415, 1981.
HYMAN, A. L., SPANNHAKE, E. W., AND KADOWITZ, P. J.: Pharmacology of the pulmonary circulation. Prog. Cardiol. **11:** 107–130, 1982.
IGNARRO, L. J., BUGA, G. M., AND CHAUDHURI, G.: EDRF generation and release from perfused bovine pulmonary artery and vein. Eur. J. Pharmacol. **149:** 79–88, 1988a.
IGNARRO, L. J., BYRNES, R. E., BUGA, G. M., AND WOOD, K. S.: Mechanisms of endothelium-dependent vascular smooth relaxation elicited by bradykinin and VIP. Am. J. Physiol. **253:** H1074–H1082, 1987a.
IGNARRO, L. J., BYRNS, R. E., BUGA, G. M., AND WOOD, K. S.: Endothelium-derived relaxing factor from pulmonary artery and vein possesses pharmacologic and chemical properties identical to those of nitric oxide radical. Circ. Res. **61:** 866–879, 1987b.
IGNARRO, L. J., BYRNS, R. E., AND WOOD, K. S.: Endothelium-dependent modulation of cGMP levels and intrinsic smooth muscle tone in isolated bovine intrapulmonary artery and vein. Circ. Res. **60:** 82–92, 1987c.
IGNARRO, L. J., BYRNS, R. E., AND WOOD, K. S.: Biochemical and pharmacological properites of endothelium-derived relaxing factor and its similarity to nitric oxide radical. *In* Vasodilatation: Vascular Smooth Muscle, Peptides, Autonomic Nerves and Endothelium, ed. by P. M. Vanhoutte, pp. 427–436, Raven Press, New York, 1988b.
INAGAMI, T.: Atrial natriuretic factor. J. Biol. Chem. **264:** 3043–3046, 1989.
INBAR, S., SCHRADER, B. J., KAUFMANN, E., VESTAL, R. E., AND RICH, S.: Effects of adenosine in combination with calcium channel blockers in patients with primary pulmonary hypertension. J. Am. Coll. Cardiol. **21:** 413–418, 1993.
INGRAM, R. H.: Effects of carotid artery occlusion and lung inflation on the main pulmonary artery. Proc. Soc. Exp. Biol. Med. **140:** 1424–1428, 1972.
INGRAM, R. H. J., SZIDON, J. P., AND FISHMAN, A. P.: Response of the main pulmonary artery of dogs to neurally released versus blood-born norepinephrine. Circ. Res. **26:** 249–262, 1970.
INGRAM, R. H., SZIDON, J. P., SKALAK, R., AND FISHMAN, A. P.: Effects of sympathetic nerve stimulation on the pulmonary arterial tree of the isolated lobe perfused in situ. Circ. Res. **22:** 801–815, 1968.
INOUE, T., AND KANNAN, M. S.: Nonadrenergic and noncholinergic excitatory neurotransmission in rat intrapulmonary artery. Am. J. Physiol. **254:** H1142–H1148, 1988.
INOUE, A., YANAGISAWA, M., KIMURA, S., KASUYA, Y., MIYAUCHI, T., GOTO, K., AND MASAKI, T.: The human endothelin family: three structually and pharmacological distinct isopeptides predicted by three separate genes. Proc. Natl. Acad. Sci. USA **86:** 2863–2367, 1989.
ITOH, H., PRATT, R. E., AND DZAU, V. J.: Atrial natriuretic polypeptide inhibits hypertrophy of vascular smooth muscle cells. J. Clin. Invest. **86:** 1690–1697, 1990.
JANAKIDEVI, K., FISHER, M. A., DEL VECCHIO, P. J., TIRUPPATHI, C., FIGGE, J., AND MALIK, A. B.: Endothelin-1 stimulates DNA synthesis and proliferation of pulmonary artery smooth muscle cells. Am. J. Physiol. **263:** C1295–C1301, 1992.
JANSEN, T. L., MORICE, A. H., AND BROWN, M. J.: A comparison of the vasodilator responses to atrial peptides in the pulmonary and renal arteries of the pig in vitro. Br. J. Pharmacol. **91:** 687–691, 1987.
JIN, H., OPARIL, S., ANN, H. S., YANG, Y., AND JACKSON, R. M.: Hypoxia-induced inhibition of coverting enzyme activity: role in vascular regulation. J. Appl. Physiol. **63:** 1012–1018, 1987.
JIN, N., PACKER, C. S., ENGLISH, D., AND RHOADES, R. A.: Inositol triphosphate is invlved in norepinephrine-but not in hypoxia-induced pulmonary arterial contraction. Am. J. Physiol. **264:** L160–L164, 1993.
JIN, H., YANG, R-H., CHEN, Y-F., THORNTON, R. M., JACKSON, R. M., AND OPARIL, S.: Hemodynamic effects of arginine vasopressin in rats adapted to chronic hypoxia. J. Appl. Physiol. **66:** 151–160, 1989.
JIN, H., YOUNG, R-H., THORNTON, R. M., CHEN, Y-F., JACKSON, R., AND OPARIL, S.: Atrial natriuretic peptide lowers pulmonary artery pressure in hypoxia adapted rats. J. Appl. Physiol. **65:** 1729–1735, 1988.
JOHNS, R. A., LINDEN, J. M., AND PEACH, M. J.: Endothelium-dependent relaxation and cyclic GMP accumulation in rabbit pulmonary artery are selectively impaired by moderate hypoxia. Circ. Res. **65:** 1508–1515, 1989.
JOHNSON, A.: PMA-induced pulmonary edema: mechanisms of the vasoactive response. J. Appl. Physiol. **65:** 2302–2312, 1988.
JOHNSON, A., AND FERRO, T. J.: TNF-α augments pulmonary vasoconstriction via the inhibition of nitrovasodilator activity. J. Appl. Physiol. **73:** 2483–2492, 1992.
JOHNSON, A. R. AND ERDOS, E. G.: Metabolism of vasoactive peptides by human endothelial cells in culture. Angiotensin I converting enzyme (kininase II) and angiotensinase. J. Clin. Invest. **59:** 684–695, 1977.
JOHNSON, D., HURST, T., WILSON, T., MURPHY, F., SAXENA, A., TO, T., AND MAYERS, I.: N^G-monomethyl-L-arginine does not restore loss of hypoxic pulmonary vasoconstriction induced by TNF-α. J. Appl. Physiol. **75:** 618–625, 1993.
JOHNSTON, W. E., VINTEN-JOHANSEN, J., PATEL, A., AND TOMMASI, E.: Hypoxic pulmonary vasoconstrictor response with asymmetric oleic acid injury in the dog. Crit. Care Med. **17:** 647–651, 1989.
JONES, D. K., HIGENBOTTAM, T. W., AND WALLWORK, J.: Treatment of primary pulmonary hypertension intravenous epoprostenol (prostacyclin). Br. Heart J. **57:** 270–278, 1987.
JONES, K., HIGENBOTTAM, T., AND WALLWORK, J.: Pulmonary vasodilation with prostacyclin in primary and secondary pulmonary hypertension. Chest **96:** 784–789, 1989.
KAAPA, P., RAJ, J. U., IBE, B. O., AND ANDERSON, J.: Vasoconstrictor response to prostacyclin in rabbit pulmonary circulation. Respir. Physiol. **85:** 193–204, 1991.
KABINS, S. A., FRIDMAN, J., KANDELMAN, M., AND WEISBERG, H.: Effects of sympathectomy on pulmonary embolism-induced lung edema. Am. J. Physiol. **202:** 687, 1962.
KADOWITZ, P. J.: Physiological and pharmacological roles of prostaglandins. Annu. Rev. Pharmacol. **15:** 285–306, 1975.
KADOWITZ, P. J., GRUETTER, C. A., MCNAMARA, D. B., GORMAN, R. R., SPANNHAKE, E. W., AND HYMAN, A. L.: Comparative effects of endoperoxide PGH_2 and an analog on the pulmonary vascular bed. J. Appl. Physiol. **42:** 953–958, 1977.
KADOWITZ, P. J., AND HYMAN, A. L.: Effect of sympathetic nerve stimulation on pulmonary vascular resistance in the dogs. Circ. Res. **33:** 221–227, 1973.
KADOWITZ, P. J., AND HYMAN, A. L.: Comparative effects of thromboxane B2 on the canine and feline pulmonary vascular bed. J. Pharmacol. Exp. Ther. **213:** 300–305, 1980.
KADOWITZ, P. J., JOINER, P. D., AND HYMAN, A. L.: Influence of sympathetic stimulation and vasoactive substance on canine pulmonary veins. J. Clin. Invest. **56:** 356–365, 1975.
KADOWITZ, P. J., KNIGHT, D. S., GREENBERG, S., AND HYMAN, A. L.: Structure and function of the adrenergic nerves in the canine pulmonary vascular bed. Methods Find. Exp. Clin. Pharmacol. **3:** 347–359, 1981.
KADOWITZ, P. J., KNIGHT, D. S., HIBBS, R. G., ELLISON, J. P., JOINER, P. D., BRODY, M. J., AND HYMAN, A. L.: Influence of 5- and 6-hydroxydopamine on adrenergic transmission and nerve terminal morphology in the canine pulmonary vascular bed. Circ. Res. **39:** 191–199, 1976.
KAI, T.: Study on the distribution of sympathetic nerves using the Falck-Hillarp's method. Bull. Chest Dis. Res. Inst. Kyoto Univ. **2:** 225–259, 1969.
KAJIOKA, S., NAKASHIMA, M., KITAMURA, K., AND KURIYAMA, H.: Mechanisms of vasodilation induced by potassium-channel activators. Clin. Sci. **81:** 129–139, 1991.
KANAI, Y., HORI, S., TANAKA, T., YASUOKA, M., WATANABE, K., AIKAWA, N., AND HOSODA, Y.: Role of 5-hydroxytryptamine in the progression of monocromtaline induced pulmonary hypertension in rats. Cardiovasc. Res. **27:** 1619–1623, 1993.
KANE, D. W., TESAURO, T., KOIZUMI, T., GUPTA, R., AND NEWMAN, J. H.:

Exercise induced pulmonary vasoconstriction during combined blockade of nitric oxide synthase and beta-adrenergic receptors. J. Clin. Invest. **93:** 677–683, 1994.

KANG, K. H., MORROW, J. D., ROBERTS I. I., J., NEWMAN, J. H., AND BANERJEE, M.: Airway and vascular effects of 8-epi-prostaglandin F2α in isolated perfused rat lung. J. Appl. Physiol. **74:** 460–465, 1993.

KARIYA, K., AND TAKAI, Y.: Distinct functions of down-regulation sensitive and resistant type of protein kinase C in rabbit aortic smooth muscle cells. FEBS Lett. **219:** 119–124, 1987.

KATO, M., AND STAUB, N. C.: Response of small pulmonary arteries to unilobar hypoxia and hypercapnia. Circ. Res. **19:** 426–440, 1966.

KAUFMAN, M. P., COLERIDGE, H. M., COLERIDGE, J. C., AND BAKER, D. G.: Bradykinin stimulates afferent vagal C-fibers in intrapulmonary airways of dogs. J. Appl. Physiol. **48:** 511–517, 1980.

KAWAGUCHI, H., SAWA, H., AND YASUDA, H.: Endothelin stimulates angiotensin I to angiotensin II conversion in cultured pulmonary artery endothelial cells. J. Mol. Cell. Cardiol. **22:** 839–842, 1990.

KAWAMURA, K., SMITH, T. L., ZHOU, Q., AND KUMMEROW, F. A.: Neuropeptide Y stimulates prostacyclin production in porcine vascular endothelial cells. Biochem. Biophys. Res. Commun. **179:** 309–313, 1991.

KAWASAKI, H., SAITO, A., AND TAKASAKI, K.: Age-related decrease of calcitonin gene-related peptidecontaining vasodilator innervation in the mesenteric resistance vessel of the spontaneously hypertensive rat. Circ. Res. **67:** 733–743, 1990.

KEALEY, G. P., AND BRODY, M. J.: Studies on the mechanism of pulmonary vascular responses to miliary pulmonary embolism. Circ. Res. **41:** 807–814, 1977.

KELLER, C. A., SHEPARD, J. W., JR., CHUN, D. S., DOLAN, G. F., VASQUEZ, P., AND MINH, V. D.: Effects of hydralazine on hemodynamics, ventilation, and gas exchange in patients with chronic obstructive pulmonary disease and pulmonary hypertension. Am. Rev. Respir. Dis. **130:** 606–611, 1984.

KENNEDY, T. P., MICHAEL, J. R., HUANG, C. K., KALLMAN, C. H., ZAHKA, K., SCHLOTT, W., AND SUMMER, W.: Nifedipine inhibits hypoxic pulmonary vasoconstriction during rest and exercise in patients with chronic obstructive pulmonary disease. A controlled double-blind study. Am. Rev. Respir. Dis. **129:** 544–551, 1984.

KENTERA, D., SUSIC, D., CVETKOVIC, A., AND DJORDJEVIC, G.: Effects of SQ 14.225, an orally active inhibitor of angiotensin-converting enzyme, on hypoxic pulmonary hypertension and right ventricular hypertrophy in rats. Basic Res. Cardiol. **76:** 344–351, 1981.

KHOSSEIN, A., MUKHARLIAMOV, N. M., MAREEV, V. I., LOBOVA, N. M., AND AGEEV, F. T.: Long-term use of the calcium antagonist nifedipine (corinfar) in the treatment of patients with primary pulmonary hypertension. Kardiol. **28:** 54–58, 1988.

KILBOURN, R. G., GROSS, S. S., JUBRAN, A., ADAMS, J., GRIFFITH, O. W., LEVI, R., AND LODATO, R. F.: N^G-monomethyl-L-arginine inhibits tumor necrosis factor-induced hypotension: implications for involvement of nitric oxide. Proc. Natl. Acad. Sci. USA **87:** 3629–3632, 1990.

KINSELLA, J. P., NEISH, S. R., SHAFFER, E., AND ABMAN, S. H.: Low-dose inhalational nitric oxide in persistent pulmonary hypertension of the new born. Lancet **340:** 819–820, 1992.

KIRBER, M. T., ORDWAY, R. W., CLAPP, L. H., WALSH, J. V., JR., AND SINGER, J. J.: Both membrane stretch and fatty acids directly activate large conductance Ca^{2+}-activated K^+ channels in vascular smooth muscle cells. FEBS Lett. **297:** 24–28, 1992.

KLIMASCHEWKI, L., KUMMER, W., MAYER, B., COURAUD, J. Y., PREISSLER, U., PHILIPPIN, B., AND HEYM, C.: Nitric oxide synthase in cardiac nrve fibers and neurons of rat ang guinea pig heart. Circ. Res. **71:** 1533–1537, 1992.

KLINGER, J. R., PETIT, R. D., CURTIN, L. A., WARBURTON, R. R., WRENN, D. S., STEINHELPER, M. E., FIELD, L. J., AND HILL, N. S.: Cardiopulmonary responses to chronic hypoxia in transgenic mice that overexpress ANP. J. Appl. Physiol. **75:** 198–205, 1993.

KNIGHT, D. S., ELLISON, J. P., HIBBS, R. G., HYMAN, A. L., AND KADOWITZ, P. J.: A light and electron microscopic study of the innervation of pulmonary arteries in the cat. Anat. Rec. **201:** 513–521, 1981.

KOLLER, K. J., LOWE, D. G., BENNETT, G. L., MINAMINO, N., KANGAWA, K., MATSUO, H., AND GOEDDEL, D.: Selective activation of the B natriuretic peptide receptor by C-type natriuretic peptide (CNP). Science (Wash. DC) **252:** 120–123, 1991.

KOMORI, K. AND VANHOUTTE, P. M.: Endothelium-derived hyperpolarizing factor. Blood Vessels **27:** 238–245, 1990.

KONDURI, G. G., GERVASIO, C. T., AND THEODOROU, A. A.: Role of adenosine triphosphate and adenosine in oxygen-induced pulmonary vasodilatation in fetal lambs. Pediatr. Res. **33:** 533–539, 1993.

KONDURI, G. G., THEODOROU, A. A., MUKHOPADHYAY, A., AND DESHMUKH, D.: Adenosine triphosphate and adenosine increase the pulmonary blood flow to postnatal levels in fetal lambs. Pediatr. Res. **31:** 451–457, 1992a.

KONDURI, G. G., WOODARD, L. L., MUKHOPADHYAY, A., AND DESHMUKH, D. R.: Adenosine is a pulmonary vasodilator in newborn lambs. Am. Rev. Respir. Dis. **146:** 670–676, 1992b.

KOUREMBANAS, S., MARSDEN, P. A., MCQUILLAN, L. P., AND FALLER, D. V.: Hypoxia induces endothelin gene expression and secretion in cultured human endothelium. J. Clin. Invest. **88:** 1054–1057, 1991.

KOUREMBANAS, S., MCQUILLAN, L. P., LEUNG, G. K., AND FALLER, D. V.: Nitric oxide regulates the expression of vasoconstrictors and growth factors by vascular emdothelium under both normoxia and hypoxia. J. Clin. Invest. **92:** 99–104, 1993.

KOYAMA, T., AND HORIMOTO, M.: Blood flow reduction in local pulmonary microvessels during acute hypoxia imposed on a small fraction of the lung. Respir. Physiol. **52:** 181–189, 1983.

KUBOTA, E., HAMASAKI, Y., SATA, T., SAGA, T., AND SAID, S. I.: Autonomic innervation of pulmonary artery: evidence for a nonadrenergic noncholinergic inhibitory system. Exp. Lung Res. **14:** 349–358, 1988.

KURATOMI, Y., LEFFERTS, P. L., CHRISTMAN, R. W., PARKER, R. E., SMITH, W. G., MUELLER, R. A., AND SNAPPER, J. R.: Effect of a 5-lipoxygenase inhibitor on endotoxin-induced pulmonary dysfunction in awake sheep. J. Appl. Physiol. **74:** 596–605, 1993.

LADOUCEUR, D. M., FLYNN, M. A., KEISER, J. A., REYNOLDS, E., AND HALEEN, S. J.: ET_A and ET_B receptors coexist on rabbit pulmonary artery vascular smooth muscle mediating contraction. Biochem. Biophys. Res. Commun. **196:** 209–215, 1993.

LAKS, M. M., JURATSCH, C. E., GARNER, D., BEAZELL, J., AND CRILEY, J. M.: Acute pulmonary artery hypertension produced by distention of the main pulmonary artery in the conscious dog. Chest **68:** 807–813, 1975.

LAMONTAGNE, D., POHL, U., AND BUSSE, R.: Mechanical deformation of vessel wall and shear stress determine the basal release of endothelium-derived relaxing factor in the intact rabbit coronary vascular bed. Circ. Res. **70:** 123–130, 1992.

LANGLEBEN, D., DEMARCHIE, M., LAPORTA, D., SPANIER, A. H., SCHLESINGER, R. D., AND STEWART, D. J.: Endothelin-1 in acute lung injury and the adult respiratory distress syndrome. Am. Rev. Respir. Dis. **148:** 1646–1650, 1993.

LAPLANTE, C., TREMBLAY, B., AND MARCEAU, F.: Relaxant effect of N-formyl-methionyl-leucyl-phenylalanine on rabbit vscular strips. J. Pharmacol. Exp. Ther. **248:** 774–780, 1989.

LAUWERYNS, J. M. AND VAN RANST, L.: Calcitonin gene related peptide immunoreactivity in rat lung: light and electron microscopic study. Thorax **42:** 183–189, 1987.

LE ROUX, M. G. S AND SYCE, J. A.: The effect of ketanserin on serotonin-induced vascular responses in the isolated perfused rat lung. Eur. J. Pharmacol. **169:** 269–273, 1989.

LEE, S. H., HO, W. K., AND EARM, Y. E.: Effects of pH on calcium-activated potassium channels in pulmoanry arterial smooth muscle cells of the rabit. Kor. J. Physiol. **25:** 17–26, 1991b.

LEE, S-L., WANG, W. W., LANZILLO, J. J., AND FANBURG, B. L.: Regulation of serotonin-induced DNA synthasis of bovine pulmonary artery smooth muscle cells. Am. J. Physiol. **266:** L53–L60, 1994.

LEE, S-L., WANG, W. W., MOORE, B. J., AND FANBURG, B. L.: Dual effects of serotonin on grouth of bovine pulmonary artery smooth muscle cells in culture. Circ. Res. **68:** 1362–1368, 1991a.

LEEMAN, M., DELCROIX, M., VACHIERY, J. L., MELOT, C., AND NAEIJE, R.: Blunted hypoxic vasoconstriction in oleic acid lung injury: effect of cyclooxygenase inhibitors. J. Appl. Physiol. **72:** 251–258, 1992.

LEFFLER, C. W., HESSLER, J. R., AND GREEN, R. S.: Pulmonary and systemic effects of exogenous prostaglandin I_2 in fetal lamb. Eur. J. Pharmacol. **54:** 37–42, 1979.

LEFFLER, C. W., HESSLER, J. R., AND GREEN, R. S.: The onset of breathing at birth stimulates pulmonary vascular prostacyclin synthesis. Pediatr. Res. **18:** 938–942, 1984.

LEFFLER, C. W., HESSLER, J. R., AND TERRAGNO, N. A.: Ventilation-induced release of prostaglandin-like material from fetal lungs. Am. J. Physiol. **238:** H282–H286, 1980.

LEFFLER, C. W., TYLER, T. L., AND CASSIN, S.: Effect of indomethacin on pulmonary vascular response to ventilation of fetal goats. Am. J. Physiol. **234:** H346–H351, 1978.

LEJEUNE, P. L., VACHIERY, J-L., LEEMAN, M., BRIMIOULLE, S., HALLEMANS, R., MELOT, C., AND NAEIJE, R.: Absence of parasympathetic control of pulmonary vascular pressure-flow plots in hyperoxic and hypoxic dogs. Respir. Physiol. **78:** 123–134, 1989.

LEVINE, B. W., TALAMO, R. C., AND KAZEMI, H.: Action and metabolism of bradykinin in dog lung. J. Appl. Physiol. **34:** 821–826, 1973.

LEW, R. A., AND BAERTSCHI, A. J.: Endothelium-dependent ANP secretion in vitro. Am. J. Physiol. **263:** H1071–H1077, 1992.

LINCOLN, T. M.: Cyclic GNP and mechanisms of vasodilatation. Pharmacol. Ther. **41:** 479–502, 1989.

LINDBERG, F., AND ANDERSSON, K-E.: Vasodilator responses to alpha-atrial natriuretic peptide in isolated omental and pulmonary arteries from rabbit and man. Acta Physiol. Scand. **144:** 391–397, 1988.

LIPPTON, H. L., COHEN, G. A., MCMURTRY, I. F., AND HYMAN, A. L.: Pulmonary vasodilation to endothelin isopeptides in vivo is mediated by potassium channel activation. J. Appl. Physiol. **70:** 947–952, 1991.

LIPPTON, H. L., HAMARI, C., FENG, C. J., BAIQIANG, C., AND SUMMER, W. R.: Peptidergic regulation of the lung circulation. Crit. Care Report **1:** 266–274, 1990.

LIPPTON, H. L., HAO, Q., HAUTH, T., AND HYMAN, A. L.: Mechanisms of signal transduction for adenosine and ATP in pulmonary vascular bed. Am. J. Physiol. **262:** H926–H929, 1992.

LIPPTON, H. L., NANDIWADA, P. A., HYMAN, A. L., AND KADOWITZ, P. J.: Influence of cyclooxygenase blockade on responses to isoproterenol, bradykinin and nitroglycerin in the feline pulmonary vascular bed. Prostaglandins **28:** 253–270, 1984.

LIU, S. F., ADCOCK, I. M., BARNES P. J., AND EVANS, T. W.: Expression of inducible nitric oxide synthase mRNA in cardiovascular tissues of rats treated with lipopolysaccharide in vivo [abstract]. Am. J. Respir. Crit. Care Med. **149:** A646, 1994b.

LIU, S. F., ADCOCK, I. M., OLD, R. W., BARNES, P. J., AND EVANS, T. W.: Lipopolysaccharide treatment in vivo induces widespread tissue expression of inducible nitric oxide synthase mRNA. Biochem. Biophys. Res. Commun. **196:** 1208–1213, 1993.

LIU, S. F. AND BARNES, P. J.: Role of endothelium in the control of pulmonary vascular tone. Endothelium **2:** 11–33, 1994.

LIU, S. F., CAI, Y., EVANS, T. W., MCCORMACK, D. G., BARER, G. R., AND BARNES, P. J.: Ligustrazine is a vasodilator of human pulmonary and bronchial arteries. Eur. J. Pharmacol. **191:** 345–350, 1990.

LIU, S. F., CRAWLEY, D. E., BARNES, P. J., AND EVANS, T. W.: Endothelium derived nitric oxide inhibits pulmonary vasoconstriction in isolated blood perfused rat lungs. Am. Rev. Respir. Dis. **143:** 32–37, 1991b.

LIU, S. F., CRAWLEY, D. E., EVANS, T. W., AND BARNES, P. J.: Endogenous nitric oxide modulates adrenergic neural vasoconstriction in guinea pig pulmonary artery. Br. J. Pharmacol. **104:** 565–569, 1991a.

LIU, S. F., CRAWLEY, D. E., EVANS, T. E., AND BARNES, P. J.: Endothelium-dependent non-adrenergic non-cholinergic neural relaxation in guinea-pig pulmonary artery. J. Pharmacol. Exp. Ther. **260:** 541–548, 1992a.

LIU, S. F., CRAWLEY, D. E., ROHDE, J. A. L., EVANS, T. W., AND BARNES, P. J.: Role of nitric oxide and guanosine 3′-,5′-cyclic monophosphate in mediatory nonadrenergic noncholinergic neural relaxation in guinea-pig pulmonary arteries. Br. J. Pharmacol. **107:** 861–866, 1992b.

LIU, S. F., DEWAR, A., CRAWLEY, D. E., BARNES, P. J., AND EVANS, T. E.: Effect of tumor necrosis factor on hypoxic pulmonary vasoconstriction. J. Appl. Physiol. **72:** 1044–1049, 1992c.

LIU, S. F., HISLOP, A. A., HAWORTH, S. G., AND BARNES, P. J.: Developmental changes in endothelium-dependent pulmonary vasodilation in pigs. Br. J. Pharmacol. **106:** 324–330, 1992d.

LIU, S. F., KUO, H-P., SHEPPARD, M. N., BARNES, P. J., AND EVANS, T. W.: Vagal stimulation induces increased pulmonary vasular permeability in guinea pig. Am. J. Respir. Crit. Care Med. **149:** 744–750, 1994a.

LIU, S. F., MCCORMACK, D. G., EVANS, T. W., AND BARNES, P. J.: Characterization and distribution of P_2-purinoceptor subtypes in rat pulmonary vessels. J. Pharmacol. Exp. Ther. **251:** 1204–1210, 1989a.

LIU, S. F., MCCORMACK, D. G., EVANS, T. W., AND BARNES, P. J.: Evidence for two P_2-purinoceptor subtypes in human small pulmonary arteries. Br. J. Pharmacol. **98:** 1014–1020, 1989b.

LIZASOAIN, I., WEINER, C., KNOWLES, R. G., AND MONCADA, S.: Estrogen increase NOS activity in the fetal guinea pig brain. (abstract) Endothelium **1** (Suppl.): S6, 1993.

LOCK, J. E., OLLEY, P. M., AND COCEANI, F.: Direct pulmonary vascular responses to prostaglandins in the conscious newborn lamb. Am. J. Physiol. **238:** H631–H638, 1980.

LOIACONO, R. E., AND STORY, D. F.: Acetylcholine-induced inhibition of responses to field stimulation in rabbit pulmonary artery is unaffected by endothelium removal. J. Pharm. Pharmacol. **36:** 262–264, 1984.

LONIGRO, A. J., SPRAGUE, R. S., STEPHENSON, A. H., AND DAHMS, T. E.: Relationship of leukotriene C4 and D4 to hypoxic pulmonary vasoconstriction in dogs. J. Appl. Physiol. **64:** 2538–2543, 1988.

LOPEZ-LOPEZ, J., GONZALEZ, C., URENA, J., AND LOPEZ-BARNEO, J.: Low pO_2 selectively inhibits K^+ channel activity in chemoreceptor cells of the mammalian carotid body. J. Gen. Physiol. **93:** 1001–1015, 1989.

LOSCALZO, J.: Endothelial dysfunction in pulmonary hypertension. N. Engl. J. Med. **327:** 117–119, 1992.

LUBER-NAROD, J., KAGE, R., AND LEEMAN, S. E.: Substance P enhances the secretion of tumor necrosis factor-α from neuroglial cells stimulated with lipopolysaccharide. J. Immunol. **152:** 819–824, 1994.

LUM, H., ANDERSEN, T. T., FENTON, J. W., AND MALIK, A. B.: Thrombin receptor activation peptide induces pulmonary vasoconstriction. Am. J. Physiol. **266:** C448–C454, 1994.

LUNDBERG, J. M., FRANCO-CERECEDA, A., HUA, X., HÖKFELT, T., AND FISCHER, J. A.: Co-existence of substance P and calcitonin gene-related peptide-like immunoreactivities in sensory nerves in relation to cardiovascular and bronchoconstrictor effects of capsaicin. Eur. J. Pharmacol. **108:** 315–319, 1985.

LUPI-HERRERA, E., SANDOVAL, J., SEOANE, M., AND BIALOSTOZKY, D.: The role of hydralazine therapy for pulmonary arterial hypertension of unknown cause. Circulation **65:** 645–650, 1982.

LUPI-HERRERA, E., SEOANE, M., VERDEJO, J., GOMEZ, A., SANDOVAL, J., BARRIOS, R., AND MARTINEZ, W.: Hemodynamic effect of hydralazine in interstitial lung disease patients with cor pulmonale. Immediate and short-term evaluation at rest and during exercise. Chest **87:** 564–573, 1985.

LYNCH, J. J., FERRO, T. J., BLUMENSTOCK, F. A., BROCKENAUER, A. M., AND MALIK, A. B.: Increased endothelial albumin permeability mediated by protein kinase C activation. J. Clin. Invest. **85:** 1991–1998, 1990.

MACINTYRE, P. D., BHARGAVA, B., HOGG, K. J., GEMMILL, J. D., AND HILLIS, W. S.: Effect of subcutaneous sumatriptan, a selective 5HT1 agonist, on the systemic, pulmonary, and coronary circulation. Circulation **87:** 401–405, 1993.

MACLAGAN, J., FRYER, A. D., AND FAULKNER, D.: Identification of M1 muscarinic receptors in pulmonary sympathetic nerves in the guinea-pig by use of pirenzepine. Br. J. Pharmacol. **97:** 499–505, 1989.

MADDEN, J. A., DAWSON, C. A., AND HARDER, D. R.: Hypoxia-induced activation in small isolated pulmonary arteries from the cat. J. Appl. Physiol. **59:** 113–118, 1985.

MAGEE, F., WRIGHT, J. L., WIGGS, B. R., PARE, P. D., AND HOGG, J. C.: Pulmonary vascular structure and function in chronic obstructive pulmonary disease. Thorax **43:** 183–189, 1988.

MAGGI, C. A., PATACCHINI, R., PERRETTI, F., TRAMONTANA, M., MANZINI, S., GEPPETTI, P., AND SANTICIOLI, P.: Sensory nerves, vascular endothelium and neurogenic relaxation of the guinea-pig isolated pulmonary artery. Naunyn-Schmiedeberg's Arch. Pharmacol. **342:** 78–84, 1990.

MAK, J. C., BARANIUK, J. N., AND BARNES, P. J.: Localization of muscarinic receptor subtype mRNAs in human lung. Am. J. Respir. Cell Mol. Biol. **7:** 344–348, 1992.

MAK, J. C. AND BARNES, P. J.: Autoradiographic visualization of muscarinic receptor subtypes in human and guinea pig lung. Am. Rev. Respir. Dis. **141:** 1559–1568, 1990.

MAK, J. C., HADDAD, E-B., BUCKLEY, N. J., AND BARNES, P. J.: Visualization of muscarinic M_4 mRNA and M_4 receptor subtype in rabbit lung. Life Sci. **53:** 1501–1508, 1993.

MAK, J. C. W., AND BARNES, P. J.: Autoradiographic localization of calcitonin gene-related peptide binding sites in human and guinea pig lung. Peptides **9:** 957–964, 1988.

MALIK, A. B.: Pulmonary embolism. Physiol. Rev. **63:** 1114–1207, 1983.

MALIK, A. B.: Mechanisms of neurogenic pulmonary edema. Circ. Res. **57:** 1–18, 1985.

MALIK, A. B. AND JOHNSON, A.: Role of humoral mediators in the pulmonary vascular response to pulmonary embolism. *In* Pulmonary Vascular Physiology and Pathophysiology, ed. by E. K. Weir and J. T. Reeves, pp. 445–468, Marcel Dekker, New York, 1989.

MALIK, A. B. AND KIDD, B. S. L.: Adrenergic blockage and the pulmonary vascular response to hypoxia. Respir. Physiol. **19:** 96–106, 1973.

MALIK, A. B. AND NEWMARK, J. M.: Adrenergic mechanisms and the pulmonary vascular response to respiratory acidosis. Respiration **33:** 179, 1976.

MANN, J., FARRUKH, I. S., AND MICHAEL, J. R.: Mechanisms by which endothelin 1 induces pulmonary vasoconstriction in the rabbit. J. Appl. Physiol. **71:** 410–416, 1991.

MARKS, A. R.: Caicium channels expressed in vascular smooth muscle. Circulation **86** (Suppl. III): 61–67, 1992.

MARKES, J. D., DONNELLY, D. F., AND HADDAD, G. G.: Adenosine-induced inhibition of vagal motoneuron excitability: receptor subtype and mechanism. Am. J. Physiol. **264:** L124–L132, 1993.

MARON, M. B. AND DAWSON, C. A.: Adrenal component to pulmonary hypertension induced by elevated cerebrospinal fluid pressure. J. Appl. Physiol. **47:** 153–160, 1979.

MARSHALL, C., AND MARSHALL, B. E.: Influence of perfusate PO_2 on hypoxic pulmonary vasoconstriction in rats. Circ. Res. **52:** 691–696, 1983.

MARTIN, G. R., BOLOFO, M. L., AND GILES, H.: Inhibition of endothelium-dependent vasorelaxation by arginine analogues: a pharmacological analysis of agonist and tissue dependence. Br. J. Pharmacol. **105:** 643–652, 1992.

MARTLING, C. R.: Sensory nerves containing tachykinins and CGRP in the lower airways. Functional implications for bronchoconstriction, vasodilatation and protein extravasation. Acta Physiol. Scand. **563** (suppl.): 1–57, 1987.

MASHBURN, J. P., KONTOS, G. J. J., HASHIMOTO, K., WILSON, D. M., AND SCHAFF, H. V.: The role of neural and vasoactive mediators in the regulation of the pulmonary circulation during cardiopulmonary preservation. J. Thorac. Cardiovasc. Surg. **98:** 434–442, 1989.

MATSUKI, T. AND OHHASHI, T.: Endothelium and mechanical responses of isolated monkey pulmonary veins to histamine. Am. J. Physiol. **259:** H1032–H1037, 1990.

MAZMANIAN, G. M., BAUDET, B., BRINK, C., CERRINA, J., KIRKIACHRIAN, S., AND WEISS, M.: Methylene blue potentiates vascular reactivity in isolated rat lungs. J. Appl. Physiol. **66:** 1040–1045, 1989.

MCBRIDE, J. T., SPRINGALL, D. R., WINTER, R. J. D., AND POLAK, J. M.: Quantitative immunocytochemistry shows calcitonin-gene related peptide-like immunoreactivity in lung neuroendocrine cells is increased by chronic hypoxia in the rat. Am. J. Respir. Cell Mol. Biol. **3:** 587–593, 1990.

MCCORMACK, D. G., BARNES, P. J., AND EVANS, T. W.: Evidence against a role for platelet-activating factor in hypoxic pulmonary vasoconstriction in the rat. Clin. Sci. **77:** 439–443, 1989a.

MCCORMACK, D. G., BARNES, P. J., AND EVANS, T. W.: Purinoceptors in the pulmonary circulation of the rat and their role in hypoxic vasoconstriction. Br. J. Pharmacol. **98:** 367–372, 1989b.

MCCORMACK, D. G., CLARKE, B., AND BARNES, P. J.: Characterization of adenosine receptors in human pulmonary arteries. Am. J. Physiol. **256:** H41-H46, 1989c.

MCCORMACK, D. G., CRAWLEY, D. E., BARNES, P. J., AND EVANS, T. W.: Bleomycin-induced lung injury in rats selectively abolishes hypoxic pulmonary vasoconstriction: evidence against a role for platelet-activating factor. Clin. Sci. **82:** 259–264, 1992.

MCCORMACK, D. G., MAK, J. C., MINETTE, P., AND BARNES, P. J.: Muscarinic receptor subtypes mediating vasodilatation in the pulmonary artery. Eur. J. Pharmacol. **158:** 293–297, 1988.

McCORMACK, D. G., MAK, J. C. W., COUPE, M. O., AND BARNES, P. J.: Calcitonin gene-related peptide vasodilation of human pulmonary vessels: receptor mapping and functional studies. J. Appl. Physiol. **67:** 1265–1270, 1989d.

McCORMACK, D. G., REES, R. G., CRAWLEY, D., BARNES P. J., AND EVANS T. W.: Sensory neuropeptides and hypoxic vasoconstriction in the rat. Thorac **48:** 554–557, 1993.

McCORMACK, D. G., SALONEN, R. O., AND BARNES, P. J.: Effect of sensory neuropeptides on canine bronchial and pulmonary vessels in vitro. Life Sci. **45:** 2405–2412, 1989e.

McDONNELL, T. J., WESTCOTT, J. Y., CZARTOLOMNA, J., AND VOELKEL, N. F.: Role of peptidoleukotrieens in hypoxic pulmonary vasoconstriction in rats. Am. J. Physiol. **259:** H751–H758, 1990.

McKAY, K. O., BLACK, J. L., DIMENT, L. M., AND ARMOUR, C. L.: Functional and autoradiographic studies of endothelin-1 and endothelin-2 in human bronchi, pulmonary arteries, and airway parasympathetic ganglia. J. Cardiovasc. Pharmacol. 17 Suppl **7:** S206–S209, 1991.

McKENZIE, J. C., TANKA, I., INAGAMI, T., MISIONI, K. S., AND KLEIN, R. M.: Alterations in atrial and plasma atrial natriuretic factor (ANF) content during the development of hypoxia induced pulmonary hypertension in the rat. Proc. Soc. Exp. Biol. Med. **181:** 459–463, 1986.

McLEAN, J. R.: Pulmonary vascular innervation. In: Abnormal pulmonary circulation, ed. by E. H. Bergofsky, pp. 27–81, Churchill Livingstone, London, 1986.

McLEOD, J. D., AND PIPER, P. J.: Effect of removing the endothelium on the vascular response induced by leukotriene C4 and D4 in guinea pig isolated heart. Eur. J. Pharmacol. **212:** 67–72, 1992.

McMAHON, T. J., HOOD, J. S., BELLAN, J. A., AND KADOWITZ, P. J.: N omega-nitro-L-arginine methyl ester selectively inhibits pulmonary vasodilator responses to acetylcholine and bradykinin. J. Appl. Physiol. **71:** 2026–2031, 1991a.

McMAHON, T. J., HOOD, J. S., AND KADOWITZ, P. J.: Pulmonary vasodilator response to vagal stimulation is blocked by N omega-nitro-L-arginine methyl ester in the cat. Circ. Res. **70:** 364–369, 1992.

McMAHON, T. J., HOOD, J. S., NOSSAMAN, B. D., IBRAHIM, I. N., FENG, C. J., AND KADOWITZ, P. J.: Influence of SQ 30741 on thromboxane receptor-mediated responses in the feline pulmonary vascular bed. J. Appl. Physiol. **71:** 2012–2018, 1991b.

McMAHON, T. J., HOOD, J. S., NOSSAMAN, B. D., AND KADOWITZ, P. J.: Analysis of responses to serotonin in the pulmonary vascular bed of the cat. J. Appl. Physiol. **75:** 93–102, 1993b.

McMAHON, T. J., IGNARRO, L. J., AND KADOWITZ, P. J.: Influence of zaprinast on vascular tone and vasodilator responses in the cat pulmonary vascular bed. J. Appl. Physiol. **74:** 1704–1711, 1993a.

McMAHON, T. J., AND KADOWITZ, P. J.: Methylene blue inhibits neurogenic cholinergic vasodilator responses in the pulmonary vascular bed of the cat. Am. J. Physiol. **263:** L575–L584, 1992.

McMAHON, T. J., AND KADOWITZ, P. J.: Analysis of responses to substance P in the pulmonary vascular bed of the cat. Am. J. Physiol. **264:** H394–H402, 1993.

McMURTRY, I. F.: Angiotensin is not required for hypoxic constriction in salt solution-perfused rat lungs. J. Appl. Physiol. **56:** 375–380, 1984.

McMURTRY, I. F.: BAY K 8644 potentiates and A23187 inhibits hypoxic vasoconstriction in rat lungs. Am. J. Physiol. **249:** H741–H746, 1985.

McMURTRY, I.: Humoral control. *In* Abnormal Pulmonary Circulation, ed. by E. H. Bergofsky, pp. 83–125, Churchill Livingstone, London, 1986.

McMURTRY, I. F., DAVIDSON, B. D., AND REEVES, J. T.: Inhibition of hypoxic pulmonary vasoconstriction by calcium antagonists in isolated rat lungs. Circ. Res. **38:** 99–104, 1976.

McMURTRY, I. F., AND MORRIS, K. G.: Platelet-activating factor causes pulmonary vasodilation in the rat. Am. Rev. Respir. Dis. **134:** 757–762, 1986.

McMURTRY, I. F., MORRIS, K. G., AND PETRUN, M. D.: Blunted hypoxic vasoconstriction in lungs from short-term high-altitude rats. Am. J. Physiol. **238:** H849–H857, 1980.

MEDICAL RESEARCH COUNCIL WORKING PARTY: Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. Lancet **1:** 681–686, 1981.

MELMON, K. L., CLINE, M. J., HUGHES, T., AND NIES, A. S.: Kinins: possible mediators of neonatal circulatory changes in man. J. Clin. Invest. **47:** 1295–1302, 1968.

MEYRICK, B., CLARK, S. W., SYMONS, C., WOODGATE, D. J., AND REID, L.: Primary pulmonary hypertension. A case report including electron microscopic study. Br. J. Dis. Chest **68:** 11–20, 1974.

MICHAEL, J. R., KENNEDY, T. P., FITZPATRICK, S., AND ROSENSTEIN, B. J.: Nifedipine inhibits hypoxic pulmonary vasoconstriction during rest and exercise in patients with cystic fibrosis and cor pulmonale. Am. Rev. Respir. Dis. **130:** 516–519, 1984.

MICHAEL, J. R., SELINGER, S., PARHAM, W., BUESCHER, P., WONG, D., AND KENNEDY, T. P.: Use of calcium channel blockers in hypoxic lung disease. Chest **88:** 260S-262S, 1985.

MICHAEL, J. R., YANG, J., FARRUKH, I. S., AND GURTNER, G. H.: Protein kinase C-mediated pulmonary vasoconstriction in rabbit: role of Ca^{2+}, AA metabolites, and vasodilators. J. Appl. Physiol. **74:** 1310–1319, 1993.

MILLER, M. A., AND HALES, C. A.: Role of cytochrome P-450 in alveolar hypoxic pulmonary vasoconstriction in dogs. J. Clin. Invest. **64:** 666–673, 1979.

MILLER, R. C., MONY, M., SCHINI, V., SCHOEFFTER, P., AND STOCLET, J. C.: Endothelial mediated inhibition of contraction and increase in cyclic GMP levels evoked by the alpha-adrenoceptor agonist B-HT 920 in rat isolated aorta. Br. J. Pharmacol. **83:** 903–908, 1984.

MINKES, R. K., KVAMME, P., HIGUERA, T. R., NOSSAMAN, B. D., AND KADOWITZ, P. J.: Analysis of pulmonary and systemic vascular responses to cromakalim, an activator of K^+_{ATP} channels. Am. J. Physiol. **260:** H957–H966, 1991.

MINKES, R. K., MCMAHON, T. J., HIGUERA, T. R., MURPHY, W. A., COY, D. H., AND KADOWITZ, P. J.: Analysis of sytemic and pulmonary vascular responses to PACAP and VIP: role of adrenal catecholamine. Am. J. Physiol. **263:** H1659–H1669, 1992.

MIYAMOTO, K., AOI, K., AND KAWAKAMI, Y.: Effect of home oxygen therapy on prognosis of patients with chronic pulmonary disease associated with pulmonary hypertension. Jpn. J. Thorac. Dis. **30** (suppl.)**:** 175–179, 1992.

MIYAUCHI, T., YORIKANE, R., SAKAI, S., SAKURAI, T., OKADA, M., NISHIKIBE, M., YANO, M., YAMAGUCHI, I., SUGISHITA, Y., AND GOTO, K.: Contribution of endodgenous endothelin-1 to the progression of cardiopulmonary alternations in rats with moncrotaline-induced pulmonary hypertension. Circ. Res. **73:** 887–897, 1993.

MOHRI, K., TAKEUCHI, K., SHINOZUKA, K., BJUR, R. A., AND WESTFALL, D. P.: Simultaneous determination of nerve-induced adenine nucleotides and nucleosides released from rabbit pulmonary artery. Anal. Biochem. **210:** 262–267, 1993.

MOLDERINGS, G. J., LIKUNGU, J., HENTRICH, F., AND GOTHERT, M.: Facilitatory presynaptic angiotensin receptors on the sympathetic nerves of the human saphenous vein and pulmonary artery. Potential involvement in beta-adrenoceptor-mediated facilitation of noradrenaline release. Naunyn-Schmiedeberg's Arch. Pharmacol. **338:** 228–233, 1988.

MONCADA, S., PALMER, R. M., AND HIGGS, E. A.: Nitric oxide: physiology, pathophysiology, and pharmacology. Pharmacol. Rev. **43:** 109–142, 1991.

MOOKHERJEE, S., ASHUTOSH, K., DUNSKY, M., HILL, N., VARDAN, S., SMULYAN, H., AND WARNER, R.: Nifedipine in cor pulmonale: acute and relatively long-term effects. Clin. Pharmacol. Ther. **44:** 289–296, 1988.

MOORE, L. G.: Circulation in the pregnancy and nonpregnancy state. *In* Pulmonary Vascular Physiology and Pathophysiology, ed. by E. K. Weir and J. T. Reeves, pp. 135–172, Marcel Dekker, New York, 1989.

MORGAN, B. C., CHURCH, S. C., AND GUNTHEROTH, W. G.: Hypoxic constriction of small pulmonary artery and vein in intact dogs. J. Appl. Physiol. **25:** 356–361, 1968.

MORGAN, J. M., GRIFFITHS, M., DU BOIS, R. M., AND EVANS, T. W.: Hypoxic pulmonary vasoconstriction in systemic sclerosis and primary pulmonary hypertension. Chest **99:** 551–556, 1991a.

MORGAN, J. M., MCCORMACK, D. G., GRIFFITHS, M. J., MORGAN, C. J., BARNES, P. J., AND EVANS, T. W.: Adenosine as a vasodilator in primary pulmonary hypertension. Circulation **84:** 1145–1149, 1991b.

MORGANROTH, M. L., REEVES, J. T., MURPHY, R. C., AND VOELKEL, N. F.: Leukotriene synthesis and receptor blockers block hypoxic pulmonary vasoconstriction. J. Appl. Physiol. **56:** 1340–1346, 1984.

MORIN, F. C., EGAN, E. A., FERGUSON, W., AND LUNDGREN, C. E.: Development of pulmonary vascular response to oxygen. Am. J. Physiol. **254:** H542–H546, 1988.

MORITOKI, H., HISAYAMA, T., TAKEUCHI, S., MIYANO, H., AND KONDOH, W.: Involvement of nitric oxide pathway in the PAF-induced relaxation of rat thoracic aorta. Br. J. Pharmacol. **107:** 196–201, 1992.

MORLEY, T. F., ZAPPASODI, S. J., BELLI, A., AND GIUDICE, J. C.: Pulmonary vasodilator therapy for chronic obstructive pulmonary disease and cor pulmonale. Treatment with nifedipine, nitroglycerin, and oxygen. Chest **92:** 71–76, 1987.

MULDERRY, P. K., GHATEI, M. A., RODRIGO, J., ALLEN, J. M., ROSENFELD, M. G., POLAK, J. M., AND BLOOM, S. R.: Calcitonin gene-related peptide in cardiovascular tissues of the rat. Neuroscience **14:** 947–954, 1985.

MULIK, T. J., JONSON, D. E., ELDE, R. P., AND LOCK, J. E.: Pulmonary vascular effects of bombesin and gastrin-release peptide in conscious newborn lambs. Am. J. Pathol. **55:** 1093–1097, 1983.

MURAMATSU, M., IWAMA, Y., SHIMIZU, K., ASANO, H., TOKI, Y., MIYAZAKI, Y., OKUMURA, K., HASHIMOTO, H., AND ITO, T.: Hypoxia-elicited contraction of aorta and coronary artery via removal of endothelium-derived nitric oxide. Am. J. Physiol. **263:** H1399–H1347, 1992.

MURASE, H., KOZAWA, O., MIWA, M., TOKUDA, H., KOTOYORI, J., KONDO, K., AND OISO, Y.: Regulation of proliferation by vasopressin in aortic smooth muscle cells: function of protein kinase C. J. Hypertens. **10:** 1505–1511, 1992.

MURRAY, K. J.: Cyclic AMP and mechanisms of vasodilation. Pharmacol. & Ther. **47:** 329–345, 1990.

MURRAY, T. R., CHEN, L., MARSHALL, B. E., AND MACARAK, E. J.: Hypoxic contraction of cultured pulmonary vascular smooth muscle cells. Am. J. Respir. Cell Mol. Biol. **3:** 457–465, 1990.

MURRAY, P. A., LODATO, R. F., AND MICHAEL, J. R.: Neural antagonists modulate pulmonary vascular pressure-flow plots in conscious dogs. J. Appl. Physiol. **60:** 1900–1907, 1986.

NAGAO, T. AND VANHOUTTE, P. M.: Endothelium-derived hyperpolarizing factor and endothelium-dependent relaxations. Am. J. Respir. Cell Mol. Biol. **8:** 1–6, 1993.

NAGASAKA, Y., AKUTSU, H., LEE, Y. S., FUJIMOTO, S., AND CHIKAMORI, J.: Long term favorable effect of oxygen administration on a patient with primary pulmonary hypertension. Chest **74:** 299–300, 1978.

NAGASAKA, Y., BHATTACHARYA, J., NANJO, S., GROPPER, M. A., AND STAUB, N. C.: Micropuncture measurement of lung microvascular pressure profile during hypoxia in cats. Circ. Res. **54:** 90–95, 1984.

NAKAMURA, T., AND PREWITT, R. L.: Effect of N^G-monomethyl-L-arginine on arcade arterioles of rat spinotrapezius muscles. Am. J. Physiol. **261:** H46-H52, 1991.

NAKANISHI, S.: Mammalian tachykinin receptors. Annu. Rev. Neurosci. **14:** 123–136, 1991.

NAKAO, K., OGAWA, Y., SUGA, S-I., AND IMURA, H.: Molecular biology and biochemistry of the natriuretic peptide system II: Natriuretic peptide receptors. J. Hypertens. **10:** 1111–1114, 1992.

NAKAYAMA, D. R., GELLER, D. A., LOWENSTEIN, C. J., DAVIES, P., PITT, B. R., SIMMONS, R. L., AND BILLIAR, T. R.: Cytokines and lipopolysaccharide induce nitric oxide synthase in cultured rat pulmonary artery smooth muscle. Am. J. Respir. Cell Mol. Biol. **7:** 471–476, 1992.

NANDIWADA, P. A., HYMAN, A. L., AND KADOWITZ, P. J.: Pulmonary vasodilator responses to vagal stimulation and acetylcholine in the cat. Circ. Res. **53:** 86–95, 1983.

NANDIWADA, P. A., KADOWITZ, P. J., SAID, S. I., MOJARAD, M., AND HYMAN, A. L.: Pulmonary vasodilator responses to vasoactive intestinal peptide in the cat. J. Appl. Physiol. **58:** 1723–1728, 1985.

NATHAN, C.: Nitric oxide as a secretory product of mammalian cells. FASEB J. **6:** 3051–3064, 1992.

NEELY, C. F., HAILE, D., AND MATOT, I.: Tone-dependent responses to 5-hydroxytryptamine in the feline pulmonary vascular bed are mediated by two different 5-hydroxytryptamine receptors. J. Pharmacol. Exp. Ther. **264:** 1315–1326, 1993.

NEWMAN, J. H., MCMURTRY, I. F., AND REEVES, J. T.: Blunted pulmonary pressor responses to hypoxia in blood perfused, ventilated lungs isolated from oxygen toxic rats: possible role of prostaglandins. Prostaglandins **22:** 11–20, 1981.

NEWMAN, K. B., MICHAEL, J. R., AND FELDMAN, A. M.: Phorbol ester-induced inhibition of beta-adrenergic system in pulmonary endothelium: role of a pertussis-sensitive protein. Am. J. Respir. Cell Mol. Biol. **1:** 517–523, 1989.

NISHIWAKI, K., NYHAN, D. P., ROCK, P., DESAI, P. M., PETERSON, W. P., PRIBBLE, C. G., AND MURRAY, P. A.: N omega-nitro-L-arginine and pulmonary vascular pressure-flow relationship in conscious dogs. Am. J. Physiol. **262:** H1331–H1337, 1992.

NISHIWAKI, K., NYHAN, D. P., STUART, R. S., DESAI, P. M., PETERSON, W. P., ROCK, P., PRIBBLE, C. G., AND MURRAY, P. A.: Pulmonary vascular alpha 1-adrenoreceptor activity in conscious dogs after left lung autotransplantation. J. Appl. Physiol. **74:** 733–741, 1993.

NOCTURNAL OXYGEN THERAPY TRIAL GROUP: Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease. Ann. Intern. Med. **93:** 391–398, 1980.

NOONAN, T. C. AND MALIK, A. B.: Pulmonary vascular response to leukotriene D4 in unanesthetized sheep: role of thromboxane. J. Appl. Physiol. **60:** 765–769, 1986.

NUNOKAWA, Y. AND TANAKA, S.: Interferon-gamma inhibits proliferation of rat vascular smooth muscle cells by nitric oxide generation. Biochem. Biophys. Res. Commun. **188:** 409–415, 1992.

NUSSENZVEIG, D. R., LEWICKI, J. A., AND MAACK, T.: Cellular mechanisms of the clerance function of type-C receptors of atrial natriuretic factor. J. Biol. Chem. **265:** 20952–20958, 1990.

NYHAN, D. P., CLOUGHERTY, P. W., AND MURRAY, P. A.: AVP-induced pulmonary vasodilation during specific V_1 receptor block in conscious dogs. Am. J. Physiol. **253:** H493–H499, 1987.

NYHAN, D. P., GELLER, H. S., GOLL, H. M., AND MURRAY, P. A.: Pulmonary vasoactive effects of exogenous and endogenous AVP in conscious dogs. Am. J. Physiol. **251:** H1009–H1016, 1986.

OBARA, H., KUSUNOKI, M., MORI, M., MIKAWA, K., AND IWAI, S.: The effects of various peptides on the isolated pulmonary artery. Peptides **10:** 241–243, 1989.

O'DONNELL, S. R., AND WANSTALL, J. C.: $Beta_1$ and $beta_2$ adrenoceptor-mediated responses in preparations of pulmonary artery and aorta from young and aged rats. J. Pharmacol. Exp. Ther. **228:** 733–738, 1984.

O'DONNELL, S. R., AND WANSTALL, J. C.: Responses to the beta 2-selective agonist procaterol of vascular and atrial preparations with different functional beta-adrenoceptor populations. Br. J. Pharmacol. **84:** 227–235, 1985.

OAKLEY, C., GLICK, G., LURIA, M. N., SCHREINER, J., AND YU, P. N.: Some regulatory mechanisms of the human pulmonary vascular bed. Circulation **26:** 917–930, 1962.

OBARA, H., KUSUNOKI, M., MORI, M., MIKAWA, K., AND IWAI, S.: The effects of various peptides on the isolated pulmonary artery. Peptides **10:** 241–243, 1989.

OGATA, M., OHE, M., KATAYOSE, D., AND TAKISHIMA, T.: Modulatory role of EDRF in hypoxic contraction of solated porcine pulmonary arteries. Am. J. Physiol. **263:** H691–H697, 1992.

OGAWA, Y., NAKAO, K., AND ARAI, H. ET. AL.: Molecular cloning of non-peptide-selective human endothelin receptors. Biochem. Biophys. Res. Commun. **178:** 248–255, 1991.

OHAR, J., POLATTY, C., ROBICHAUD, A., FOWLER, A., VETROVEC, G., AND GLAUSER, F.: The role of vasodilators in patients with progressive systemic sclerosis. Interstitial lung disease and pulmonary hypertension. Chest **88:** 263S–265S, 1985.

OHAR, J. A., PYLE, J. A., WALLER, K. S., MYERS, T. M., WEBSTER, R. O., AND LAGUNOFF, D. A.: A rabbit model of pulmonary hypertension induced by synthetic platelet-activating factor acetylglyceryl ether phosphorylcholine. Am. Rev. Respir. Dis. **141:** 104–110, 1990.

OHAR, J. A., WALLER, K. S., AND DAHMS, T. E.: Platelet-activating factor induces selective pulmonary arterial hyperreactivity in isolated perfused rabbit lungs. Am. Rev. Respir. Dis. **148:** 158–163, 1993.

OHAR, J. A., WALLER, K. S., DEMELLO, D., AND LAGUNOFF, D.: Administration of chronic intravenous platelet-activating factor induces pulmonary arterial atrophy and hypertension in rabbits. Lab. Invest. **65:** 451–458, 1991.

OHLSTEIN, E. H., HOROHONICH, S., SHEBUSKI, R. J., AND RUFFOLO, R. R., JR.: Localization and characterization of $alpha_2$ adrenoceptors in the isolated canine pulmonary vein. J. Pharmacol. Exp. Ther. **248:** 233–239, 1989.

OHTAKA, H., TSANG, J. Y., FOSTER, A., HOGG, J. C., AND SCHELLENBERG, R. R.: Comparative effects of leukotrienes on porcine pulmonary circulation in vitro and in vivo. J. Appl. Physiol. **63:** 582–588, 1987.

OKA, M., HASUNUMA, K., WEBB, S. A., STELZNER, T. J., RODMAN, D. M., AND MCMURTRY, I. F.: EDRF suppresses an unidentified vasoconstrictor mechanism in hypertensive rat lungs. Am. J. Physiol. **264:** L587–L597, 1993.

OKABE, K., KITAMURA, K., AND KURIYAMA, H.: Features of 4-aminopyridine sensitive outward curent observed in single smooth muscle cells from rabbit pulmonary artery. Pfluegers Arch. Eur. J. Physiol. **409:** 561–568, 1987.

OKPAKA, D. T.: A dual action of histamine on guinea-pig lung vessels. Br. J. Pharmacol. **45:** 311–321, 1972.

OLSON, N. C., ROBINSON, N. E., ANDERSON, D. L., AND SCOTT, J. B.: Effect of carotid body hypoxia and/or hypercapnia on pulmonary vascular resistance. Pro. Soc. Exp. Biol. Med. **170:** 188–193, 1982.

OLSSON, R. A., AND PEARSON, J. D.: Cardiovascular purinoceptors. Physiol. Rev. **70:** 761–845, 1990.

ONIZUKA, M., MIYAUCHI, T., MORITA, R., AKAOGI, E., MITSUI, K., SUZUKI, N., FUJINO, M., YANAGISAWA, M., GOTO, K., MASAKI, T., AND HORI, M.: Increased plasma concentrations of endothelin-1 during and after pulmonary surgery. J. Cardiovasc. Pharmacol. **17** (Suppl. 7)**:** S402–S403., 1991.

ONO, S., WESTCOTT, J. Y., AND VOELKEL, N. F.: PAF antagonists inhibits pulmonary vascular remodeling induced by hypobaric hypoxia in rats. J. Appl. Physiol. **73:** 1084–1092, 1992.

ORTIZ, J. L., LABAT, C., NOREL, X., GORENNE, I., VERLEY, J., AND BRINK, C.: Histamine receptors on human isolated pulmonary arterial muscle preparations: effects of endothelial cell removal and nitric oxide inhibitors. J. Pharmacol. Exp. Ther. **260:** 762–767, 1992.

ORTON, E. C., RAFFESTIN, B., AND MCMURTRY, I. F.: Protein kinase influences rat pulmonary vascular reactivity. Am. Rev. Respir. Dis. **141:** 654–658, 1990.

ORTON, E. C., REEVES, J. T., AND STENMARK, K. R.: Pulmonary vasodilation with structurally altered pulmonary vessels and pulmonary hypertension. J. Appl. Physiol. **65:** 2459–2467, 1988.

PACE, J. B.: Sympathetic control of pulmonary vascular impedance in anesthetized dogs. Circ. Res. **29:** 555–568, 1971.

PACE, J. B.: Influence of carotid occlusion on pulmonary vascular resistance in anesthetized dogs. Proc. Soc. Exp. Biol. Med. **158:** 215, 1978.

PACKER, M., GREENBERG, B., MASSIE, B., AND DASH, H.: Deleterious effects of hydralazine in patients with primary pulmonary hypertension. N. Engl. J. Med. **306:** 1326–1331, 1982.

PACKER, M., MEDINA, N., AND YUSHAK, M.: Adverse hemodynamic and clinical effects of calcium channel blockade in pulmonary hypertension secondary to obliterative pulmonary vascular disease. J. Am. Coll. Cardiol. **4:** 890–901, 1984.

PALEVSKY, H. I., LONG, W., CROW, J., AND FISHMAN, A. P.: Prostacyclin and acetylcholine as screening agents for acute pulmonary vasodilator responsiveness in primary pulmonary hypertension. Circulation **82:** 2018–2026, 1990.

PALMER, R. M. J., FERRIDGE, A. G., AND MONCADA, S.: Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor. Nature (Lond.) **327:** 524–526, 1987.

PALMISANO, J. M., MARTIN, J. M., KRAUZOWICZ, B. A., TRUMAN, K. H., AND MELIONES, J. N.: Effects of supplemental oxygen administration in an infant with pulmonary artery hypertension. Heart & Lung **19:** 627–630, 1990.

PANG, I. M., O'BRODOVICH, H. M., MELLINS, R. B., AND STALCUP, S. A.: Bradykinin-induced increase in pulmonary vascular permeability in hypoxic sheep. J. Appl. Physiol. **52:** 370–375, 1982.

PARK, M. K., ZAKHEIM, R. M., MATTIOLI, L., AND SUNDERSON, J.: Altered reactivity of rat pulmonary arterial smooth muscle to vasoactive agents in hypoxia. Proc. Soc. Exp. Biol. Med. **155:** 274–277, 1977.

PARTANEN, M., LAITINEN, A., HERWONEN, A., TOIVANEN, M., AND LAITINEN, L. A.: Catecholamine and acetylcholinesterase containing nerves in human lower respiratory tract. Histochemistry **76:** 175–188, 1982.

PARTANEN, J., NIEMINEN, M. S., AND LUOMANMAKI, K.: Death in a patient with primary pulmonary hypertension after 20 mg of nifedipine. N. Engl. J. Med. **328:** 812, 1993.

PASCUAL, J. M., FIORELLI, A. I., BELLOTTI, G. M., STOLF, N. A., AND JATENE, A. D.: Prostacyclin in the management of pulmonary hypertension after heart transplantation. J. Heart Transplant. **9:** 644–651, 1990.

PATERSON, N. A., HAMILTON, J. T., YAGHI, A., AND MILLER, D. S.: Effect of hypoxia on responses of respiratory smooth muscle to histamine and LTD_4. J. Appl. Physiol. **64:** 435–440, 1988.

PATY, P. S., SHERMAN, P. F., SHEPARD, J. M., MALIK, A. B., AND KAPLAN, J. E.: Role of adenosine in platelet-mediated reduction in pulmonary vascular permeability. Am. J. Physiol. **262:** H771–H777, 1992.

PAWLOSKI, J. R., AND CHAPNICK, B. M.: Leukotriene C4 and D4 are potent endothelium-dependent ralaxing agent in canine splanchnic venous capacitance vessels. Circ. Res. **73:** 395–404, 1993.

PEACH, M. J., JOHNS, R. A., AND ROSE, C. E. J.: The potential role of interactions between endothelium and smooth muscle in pulmonary vascular physiology and pathophysiology. *In* Pulmonary Vascular Physiology and Pathophysiology, ed. by E. K. Weir and J. T. Reeves, pp. 643–697, Marcel Dekker, New York, 1989.

PEACOCK, A. J., DAWES, K. E., SHOCK, A., GRAY, A. J., REEVES, J. T., AND LAURENT, G. J.: Endothelin-1 and endothelin-3 induce chemotaxis and replication of pulmonary fibroblasts. Am. J. Resp. Cell Mol. Biol. **7:** 492–499, 1992.

PEARL, R. G.: Inhaled nitric oxide. Anesthesiology **78:** 413–416, 1993.

PEPKE-ZABA, J., HIGENBOTTAM, T. W., DINH-XUAN, A. T., RIDDEN, C., AND KEALEY, T.: α-Adrenoceptor stimulation of porcine pulmonary arteries. Eur. J. Pharmacol. **235:** 169–175, 1993.

PEPKE-ZABA, J., HIGENBOTTAM, T., DINH-XUAN, A., STONE, D., AND WALLWORK, J.: Inhaled nitric oxide as a cause of selective pulmonary vasodilatation in pulmonary hypertension. Lancet **338:** 1173–1174, 1991.

PERREAULT, T., COE, J. Y., OLLEY, P. M., AND COCEANI, F.: Pulmonary vascular effects of prostaglandin D_2 in newborn pig. Am. J. Physiol. **258:** H1292–H1299, 1990.

PERREAULT, T., AND DE MARTE, J.: Endothelin-1 has a dilator effect on neonatal pig pulmonary vasculature. J. Cardiovasc. Pharmacol. **18:** 43–50, 1991.

PERREAULT, T., AND DE MARTE, J.: Maturational changes in endothelium-derived rlaxations in newborn piglet pulmonary circulation. Am. J. Physiol. **264:** H302–H309, 1993.

PERRY, M., AND TAYLOR, A. E.: Phorbol myristateacetate-induced injury of isolated perfused rat lungs: neutrophill dependence. J. Appl. Physiol. **65:** 2164–2169, 1988.

PESSACQ, T. P.: The innervation of the lung of new born children. Acta Anat. **79:** 93–101, 1971.

PIENE, H.: The influence of pulmonary blood flow rate on vascular input impedance and hydraulic power in the sympathetically and noradrenaline stimulated cat lung. Acta Physiol. Scand. **98:** 44–53, 1976.

PINHEIRO, J. M., ANDERSEN, T. T., AND MALIK, A. B.: Receptor mechanism of thrombin-mediated pulmonary vasodilation in neonates. Am. J. Physiol. **265:** L355–L359, 1993.

PONGS, O.: Molecular biology of voltage-dependent potassium channels. Physiol. Rev. **72** (suppl.): S69–S88, 1992.

POST, J. M., HUME, J. R., ARCHER, S. L., AND WEIR, E. K.: Direct role for potassium channel inhibition in hypoxic pulmonary vasoconstriction. Am. J. Physiol. **262:** C882–C890, 1992.

PREVOST, M. C., CARIVEN, C., SIMON, M. F., CHAP, H., AND DONSTE-BLAZY, L.: Platelet-activating factor (PAF-acether) is released into rat pulmonary alveolar fluid as a consequence of hypoxia. Biochem. Biophys. Res. Commun. **119:** 58–63, 1984.

PRICE, K. C.: Pulmonary vasomotion resulting from miliary embolism of the lungs. Am. J. Physiol. **182:** 183–190, 1955.

PRITZE, S., SIMMET, T., AND PESKAR, B. A.: Effect of platelet-activating factor on porcine pulmonary blood vessels in vitro. Naunyn-Schmiedeberg's Arch. Pharmacol. **344:** 495–499, 1991.

QUAST, U.: Do K^+ channel openers relax smooth muscle by opening K^+ channels? Trends Pharmacol. Sci. **14:** 332–337, 1993.

QUEBBEMAN, E. J. AND DAWSON, C. A.: Effect of lung inflation and hypoxia on pulmonary arterial blood volume. J. Appl. Physiol. **43:** 8–13, 1977.

QUINN, A. C. AND VALLANCE, P.: Inhaled nitric oxide-from pollutant to patent. Eur. J. Clin. Invest. **23:** 445–447, 1993.

RABINOVITCH, M., BOTHWELL, T., HAYAKAWA, B. N., WILLIAM, W. G., TRUSLER, G. A., ROWE, R. D., OLLEY, P. M., AND CUTZ, E.: Pulmonary artery endothelial abnormalities in patients with cogenital heart defects and pulmonary hypertension. Lab. Invest. **55:** 632–653, 1986.

RABINOVITCH, M., MULLEN, M., ROSENBERG, H. C., MARUYAMA, K., O'BRODOVICH, H., AND OLLEY, P. M.: Angiotensin II prevents hypoxic hypertension and vascular changes in rat. Am. J. Physiol. **254:** H500–H508, 1988.

RADERMACHER, P., SANTAK, B., WUST, H. J., TARNOW, J., AND FALKE, K. J.: Prostacyclin for the treatment of pulmonary hypertension in the adult respiratory distress syndrome: effects on pulmonary capillary pressure and ventilation-perfusion distributions [see comments]. Anesthesiology **72:** 238–244, 1990.

RAFFESTIN, B., CERRINA, J., BOULLET, C., LABAT, C., BENVENISTE, J., AND BRINK, C.: Response and sensitivity of isolated human pulmonary muscle preparations to pharmacological agents. J. Pharmacol. Exp. Ther. **233:** 186–194, 1985.

RAFFESTIN, B., LEVAME, M., EDDAHIBI, S., VIOSSAT, I., BRAQUET, P., CHABRIER, P. E., CANTIN, M., AND ADNOT, S.: Pulmonary vasodilatory action of endogenous atrial natriuretic factor in rats with hypoxic pulmonary hypertension. Effects of monoclonal atrial natriuretic factor antibody. Circ. Res. **70:** 184–192, 1992.

RAND, M. J.: Nitrergic transmission: nitric oxide as a mediator of non-adrenergic, non-cholinergic neuro-effector transmission. Clin. Exp. Pharmacol. Physiol. **19:** 147–169, 1992.

RAUD, J., LUMDEBERG, T., BRODDA-JANSEN, G., THEODORSSON, E., AND HEDQVIST, P.: Potent anti-inflammatory action of calcitonin gene-related peptide. Biochem. Biophys. Res. Commun. **180:** 1429–1435, 1991.

REES, D. D., PALMER, R. M., AND MONCADA, S.: Role of endothelium-derived nitric oxide in the regulation of blood pressure. Proc. Natl. Acad. Sci. USA **86:** 3375–3378, 1989.

REEVES, J. T., DEMPSEY, J. A., AND GROVER, R. F.: Pulmonary circulation during exercise. *In* Pulmonary Vascular Physiology and Pathophysiology, ed. by E. K. Weir and J. T. Reeves, pp. 107–133, Marcel Dekker, New York, 1989.

REEVES, J. T., AND GROVER, R. F.: Blockade of acute hypoxic pulmonary hypertension by endotoxin. J. Appl. Physiol. **36:** 328–332, 1974.

REEVES, J. T., GROVES, B. M., AND TURKEVICH, D.: Controversies in medicine: the case for the treatment selected patients with primary pulmonary hypertension. Am. Rev. Respir. Dis. **134:** 342–346, 1986.

REID, P. G., FRASER, A., WATT, A., HENDERSON, A., AND ROUTLEGE, P.: Acute hemodynamic effects of intraveneous infusion of adenosine in concious man. Eur. Heart J. **11:** 1018–1028, 1990.

RENGASAMY, A. AND JOHNS, R. A.: Characterization of endothelium-derived relaxing factor/nitric oxide synthase from bovine cerebellum and mechanism of modulation by high and low oxygen tensions. J. Pharmacol. Exp. Ther. **259:** 310–316, 1991.

REVEST, P. A., AND ABBOTT, N. J.: Membrane ion channels of endothelial cells. Trends Pharmacol. Sci. **13:** 404–407, 1992.

RHODIN, J. A.: Microscopic anatomy of the pulmonary vascular bed in the cat lung. Microvasc. Res. **15:** 169–193, 1978.

RICH, S., BRUNDAGE, B. H., AND LEVY, P. S.: The effect of vasodilator therapy on the clinical outcome of patients with primary pulmonary hypertension. Circulation **71:** 1191–1196, 1985.

RICH, S., GANZ, R., AND LEVY, P. S.: Comparative actions of hydralazine, nifedipine and amrinone in primary pulmonary hypertension. Am. J. Cardiol. **52:** 1104–1107, 1983b.

RICH, S., KAUFMANN, E., AND LEVY, P. S.: The effect of high doses of calcium-channel blockers on survial in primary pulmonary hypertension. N. Engl. J. Med. **327:** 76–81, 1992.

RICH, S., MARTINEZ, J., LAM, W., LEVY, P. S., AND ROSEN, K. M.: Reassessment of the effects of vasodilator drugs in primary pulmonary hypertension: guidelines for determining a pulmonary vasodilator response. Am. Heart J. **105:** 119–127, 1983a.

RICH, G. F., MURPHY, G. D., JR., ROOS, C. M., AND JOHNS, R. A.: Inhaled nitric oxide. Selective pulmonary vasodilation in cardiac surgical patients. Anesthesiology **78:** 1028–1035, 1993.

RICHALET, J. P., HORNYCH, A., RATHAT, C., AUMONT, J., LARMIGNAT, P., AND REMY, P.: Plasma prostaglandins, leukotrienes and thromboxane in acute high altitude hypoxia. Respir. Physiol. **85:** 205–215, 1991.

RICHARDSON, J. B.: Nerve supply to the lung. Am. Rev. Respir. Dis. **119:** 785–802, 1979.

ROBERTS, J. D., CHEN, T-Y., KAWAI, N., WAIN, J., DUPUY, P., SHIMOUCHI, A., BLOCH, K., POLANER, D., AND ZAPOL, W. M.: Inhaled nitric oxide reverses pulmonary vasoconstriction in the hypoxic and acidotic newborn lamb. Circ. Res. **72:** 246–254, 1993a.

ROBERTS, J. D., LANG, P., BIGATELLO, L. M., VLAHAKES, G. J., AND ZAPOL, W. M.: Inhaled nitric oxide in congenital heart disease. Circulation **87:** 447–453, 1993b.

ROBERTS, J. D., POLANER, D. H., LANG, P., AND ZAPOL, W. M.: Inhaled nitric oxide in persistent pulmonary hypertension of the newborn. Lancet **340:** 818–819, 1992.

ROBERTSON, B. E., KOZLOWSKI, R. Z., AND NYE, P. C.: Opposing actions of tolbutamide and glibenclamide on hypoxic pulmonary vasoconstriction. Comp. Biochem. Physiol. Comp. Pharmacol. Toxicol. **102:** 459–462, 1992.

ROBIN, E. D.: Some basic and clinical challenges in the pulmonary circulation. Chest **81:** 357–363, 1982.

ROBIN, E. D., THEODORE, J., BURKE, C. M., OESTERLE, S. N., FOWLER, M. B., JAMIESON, S. W., BALDWIN, J. C., MORRIS, A. J., HUNT, S. A., VANKESSEL, A.: Hypoxic pulmonary vasoconstriction persists in the human transplanted lung. Clin. Sci. **72:** 283–287, 1987.

RODMAN, D. M.: Chronic hypoxia selectively augments rat pulmonary artery Ca^{2+} and K^+ channel-mediated relaxation. Am. J. Physiol. **263:** L88-L94, 1992.

RODMAN, D. M., STELZER, T. J., ZAMORA, M. R., BONVALLET, S. T., OKA, M., SATO, K., O'BRIEN, R. F., AND MCMURTRY, I. F.: Endothelin increases the pulmonary microvascular pressure and causes pulmonary edema in salt solution but not blood-perfused rat lungs. J. Cardiovasc. Pharmacol. **20:** 658–663, 1992.

RODMAN, D. M., YAMAGUCHI, T., HASUNUMA, K., O'BRIEN, R. F., AND MCMURTRY, I. F.: Effects of hypoxia on endothelium-dependent relaxation of rat pulmonary artery. Am. J. Physiol. **258:** L207–L214, 1990.

RODMAN, D. M., YAMAGUCHI, T., O'BRIEN, R. F., AND MCMURTRY, I. F.: Hypoxic contraction of isolated rat pulmonary artery. J. Pharmacol. Exp. Ther. **248:** 952–959, 1989.

RODRIGUEZ-ROISIN, R., ROCA, J., AGUSTI, A. G., MASTAI, R., WAGNER, P. D., AND BOSCH, J.: Gas exchange and pulmonary vascular reactivity in patients with liver cirrhosis. Am. Rev. Respir. Dis. **135:** 1085–1092, 1987.

RONCALLI, M., SPRINGALL, D. R., MAGGIONI, M., MORADOGHLI-HAFTVANI, A., WINTER, R. J. D., ZHAO, L., COGGI, G., AND POLAK, J. M.: Early changes in the calcitonin gene-related peptide (CGRP) content of pulmonary endocrine cells concomitant with vascular remodeling in hypoxic rat. Am. J. Resp. Cell Mol. Biol. **9:** 467–474, 1993.

ROSENBERG, H., MULLEN, M., AND RABINOVITCH, M.: Increased pulmonary vascular reactivity in monocrotaline model of endothelial injury (abstract). Am. Rev. Respir. Dis. **131:** A410, 1985.

ROSSIANT, R., FALKE, K. J., LOPEZ, F., SLAMA, K., PISON, U., AND ZAPOL, W. M.: Inhaled nitric oxide for the adult respiratory distress syndrome. N. Engl. J. Med. **328:** 399–405, 1993.

ROUNDS, S., FARBER, H. W., HILL, N. S., AND O'BRIEN, R. F.: Effects of endothelial cell injury on pulmonary vascular reactivity. Chest **88** (suppl.): 213S–216S, 1985.

ROUNDS, S., AND MCMURTRY, I. F.: Inhibitors of oxidative ATP production cause transient vasoconstriction and block subsequent pressor responses in rat lungs. Circ. Res. **48:** 393–400, 1981.

ROUNDS, S. I. S.: Pulmonary circulatory control in lung injury. *In* Pulmonary Vascular Physiology and Pathophysiology, ed. by E. K. Weir and J. T. Reeves, pp. 403–468, Marcel Dekker, New York, 1989.

ROZKOVEC, A., STRADLING, J. R., SHEPHERD, G., MACDERMOT, J., OAKLEY, C. M., AND DOLLERY, C. T.: Prediction of favourable responses to long term vasodilator treatment of pulmonary hypertension by short term administration of epoprostenol (prostacyclin) or nifedipine. Br. Heart J. **59:** 696–705, 1988.

RUBANYI, G. M., ROMERO, J. C., AND VANHOUTTE, P. M.: Flow-induced release of endothelium-derived relaxing factor. Am. J. Physiol. **250:** H1145–H1149, 1986.

RUBIN, L. J.: Calcium channel blockers in primary pulmonary hypertension. Chest **88** (suppl.): 257S–260S, 1985.

RUBIN, L. J., GROVES, B. M., REEVES, J. T., FROSOLONO, M., HANDEL, F., AND CATO, A. E.: Prostacyclin-induced acute pulmonary vasodilation in primary pulmonary hypertension. Circulation **66:** 334–338, 1982b.

RUBIN, L. J., HANDEL, F., AND PETER, R. H.: The effects of oral hydralazine on right ventricular end-diastolic pressure in patients with right ventricular failure. Circulation **65:** 1369–1373, 1982a.

RUBIN, L. J., MENDOZA, J., HOOD, M., MCGOON, M., BARST, R., WILLIAMS, W. B., DIEHL, J. H., CROW, J., AND LONG, W.: Treatment of primary pulmonary hypertension with continuous intravenous prostacyclin (epoprostenol). Results of a randomized trial. Ann. Intern. Med. **112:** 485–491, 1990.

RUBIN, L. J., AND MOSER, K.: Long-term effects of nitrendipine on hemodynamics and oxygen transport in patients with cor pulmonale. Chest **89:** 141–145, 1986.

RUBIN, L. J., NICOD, P., HILLIS, L. D., AND FIRTH, B. G.: Treatment of primary pulmonary hypertension with nifedipine. A hemodynamic and scintigraphic evaluation. Ann. Intern. Med. **99:** 433–438, 1983.

RUBIN, L. J., AND PETER, R. H.: Oral hydralazine therapy for primary pulmonary hypertension. N. Engl. J. Med. **302:** 69–73, 1980.

RUDOLPH, A. M.: Fetal and neonatal pulmonary circulation. Annu. Rev. Physiol. **41:** 383–395, 1979.

RUDOLPH, A. M., AND YUAN, S.: Response of the pulmonary vasculature to hypoxia and H^+ ion concentration changes. J. Clin. Invest. **45:** 399–411, 1966.

RUSS, R. D., AND WALKER, B. R.: Role of nitric oxide in vasopressinergic pulmonary vasodilatation. Am. J. Physiol. **262:** H743–H747, 1992.

RUSS, R. D., AND WALKER, B. R.: Maintained endothelium-dependent pulmonary vasodilation following chronic hypoxia in the rat. J. Appl. Physiol. **74:** 339–344, 1993.

SAADJIAN, A., PHILIP-JOET, F., AND ARNAUD, A.: Hemodynamic and oxygen delivery responses to nifedipine in pulmonary hypertansion secondary to chronic obsructive lung disease. Cardiology **74:** 196–204, 1987.

SAADJIAN, A., PHILIP-JOET, F. F., VESTRI, R., AND ARNAUD, A. G.: Long term treatment of chronic obstructive lung disease by nifedipine: an 18 month haemodynamic study. Eur. Respir. J. **1:** 716–720, 1988.

SADA, K., SHIRAI, M., AND NINOMIYA, I.: Vagally and acetylcholine-mediated constriction in small pulmonary vessels of rabbits. J. Appl. Physiol. **63:** 1601–1609, 1987.

SAID, S. I.: Metabolic function of the pulmonary circulation. Circ. Res. **50:** 325–333, 1982.

SAID, S. I.: Neuropeptides as modulators of injury and inflammation. Life Sci. **47:** L19–L21, 1990.

SAKAI, A. AND VOELKEL, N. F.: Dibutyryl cyclic adenosine monophosphate inhibits pulmonary vasoconstriction. Lung **116:** 221–231, 1988.

SAKAKIBARA, H., HASHIBA, Y., TAKI, K., KAWANISHI, M., SHIMADA, Y., AND ISHIKAWA, N.: Effects of sympathetic nerve stimulation on lung vascular permeability in the rat. Am. Rev. Respir. Dis. **145:** 685–692, 1992.

SALVATERRA, C. G., AND GOLDMAN, W. F.: Acute hypoxia increases cytosolic calcium in cultured pulmonary myocytes. Am. J. Physiol. **9:** L323–L328, 1993.

SAVINEAU, J-P., AND MARTHAN, R.: Effect of cromakalim on KCl-, noradrenaline- and angiotensin II-induced contractions in the rat pulmonary artery. Pulm. Pharmacol. **6:** 41–48, 1993.

SAVINEAU, J-P., MARTHAN, R., AND CREVEL, H.: Contraction of vascular smooth muscle induced by phorbol 12,13 dibutyrate in human and rat pulmonary arteries. Br. J. Pharmacol. **104:** 639–644, 1991.

SCHINI, V. B., BOULANGER, C., REGOLI, D., AND VANHOUTTE, P. M.: Bradykinin stimulates the production of cyclic GMP via activation of B_2 kinin receptors in cultured porcine aortic endothelial cells. J. Pharmacol. Exp. Ther. **252:** 581–585, 1990.

SCHOLZ, K. H., MARTEN, J., HERRMANN, C., SPAAR, U., TEBBA, U., NEUHAUS, K. L., AND KREUZER, H.: Atrial natriuretic factor levels and pressure in the pulmonary circulation before and after coronary dilatation. Kinisch. Wochensch. **68:** 823–829, 1990.

SCHRANZ, D., ZEPP, F., IVERSEN, S., WIPPERMANN, C., HUTH, R., ZIMMER, B., JUNGST, B. K., AND OELERT, H.: Effects of tolazoline and prostacyclin on pulmonary hypertension in infants after cardiac surgery. Crit. Care Med. **20:** 1243–1249, 1992.

SCHRAY-UTZ, B., ZEIHER, A. M., AND BUSSE, R.: Expression of constitutive NO synthase in cultured endothelial cells is enhanced by 17-β-estradiol (abstract). Endothelium **1** (suppl.): S24, 1993.

SCOTT, J. P., HIGENBOTTAM, T. W., SMYTH, R. L., AND WALLWORK, J.: Acute pulmonary hypertensive crisis in a patient with primary pulmonary hypertension treated by both epoprostenol (prostacyclin) and nitroprusside. Chest **99:** 1284–1285, 1991.

SEGEL, N., STANEK, V., JOSHI, R., AND SINGHAL, S.: The inluence of bradykinin on the pulmonary hypoxic response in normal man. *In* Progress in Respiratory Research, pp. 119–126 Basel, Karger, 1970.

SELIG, W. M., BURHOP, K. E., GARCIA, J. G., AND MALIK, A. B.: Substance P-induced pulmonary vasoreactivity in isolated perfused guinea pig lung. Circ. Res. **62:** 196–203, 1988.

SELIG, W. M., NOONAN, T. C., KERN, D. F., AND MALIK, A. B.: Pulmonary microvascular responses to arachidonic acid in isolated perfused guinea pig lung. J. Appl. Physiol. **60:** 1972–1979, 1986.

SHAUL, P. W., CAMPBELL, W. B., FARRAR, M. A., AND MAGNESS, R. R.: Oxygen modulates prostacyclin synthesis in ovine fetal pulmonary arteries by an effect on cyclooxygenase. J. Clin. Invest. **90:** 2147–2155, 1992.

SHAUL, P. W., FARRAR, M. A., AND MAGNESS, R. R.: Pulmonary endothelial nitric oxide production is developmentally regulated in the fetus and newborn. Am. J. Physiol. **265:** H1056–H1063, 1993.

SHAUL, P. W., KINANE, B., FARRAR, M. A., BUJA, L. M., AND MAGNESS, R. R.: Prostacyclin production and mediation of adenylate cyclase activity in the pulmonary artery. Alterations after prolonged hypoxia in the rat. J. Clin. Invest. **88:** 447–455, 1991.

SHAUL, P. W., MUNTZ, K. H., AND BUJA, L. M.: Comparison of beta adrenergic receptor binding characteristics and coupling to adenylate cyclase in rat pulmonary artery versus aorta. J. Pharmacol. Exp. Ther. **252:** 86–92, 1990.

SHEBUSKI, R. J., FUJITA, T., AND RUFFOLO, R. R., JR.: Evaluation of alpha-1 and alpha-2 adrenoceptor-mediated vasoconstriction in the in situ, autoperfused, pulmonary circulation of the anesthetized dog. J. Pharmacol. Exp. Ther. **238:** 217–223, 1986.

SHEBUSKI, R. J., OHLSTEIN, E. H., SMITH, J. M., JR., AND RUFFOLO, R. R., JR.: Enhanced pulmonary alpha-2 adrenoceptor responsiveness under conditions of elevated pulmonary vascular tone. J. Pharmacol. Exp. Ther. **242:** 158–165, 1987.

SHEPPARD, M. N., POLAK, J. M., ALLEN, J. M., AND BLOOM, S. R.: Neuropeptide tyosine (NPY), a newly discovered peptide, is present in the mammalian respiratory tract. Thorax **39:** 326–330, 1984.

SHIBAMOTO, T., YAMAGUCHI, Y., HAYASHI, JR.,T., SAEKI, Y., KAWAMOTO, M., AND KOYAMA, S.: PAF increases capillary pressure but not vascular permeability in isolated blood-perfused canine lungs. Am. J. Physiol. **264:** H1454–H1459, 1993.

SHIRAI, M., SADA, K., AND NINOMIYA, I.: Effects of regional alveolar hypoxia and hypercapnia on small pulmonary vessels in cats. J. Appl. Physiol. **61:** 440–448, 1986.

SHIRAI, M., SADA, K., AND NINOMIYA, I.: Nonuniform effects of histamine on small pulmonary vessels in cats. J. Appl. Physiol. **62:** 451–458, 1987.

SILOVE, E. D., AND GROVER, R. F.: Effects of alpha adrenergic blockade and tissue catecholamine depletion on pulmonary vascular response to hypoxia. J. Clin. Invest. **47:** 244–285, 1968.

SILOVE, E. D., AND SIMCHA, A. J.: Histamine-induced pulmonary vasodilatation in the calf: relationship to hypoxia. J. Appl. Physiol. **35:** 830–836, 1973.

SIM, M. K., AND MANJEET, S.: Endothelial muscarinic receptors in the rabbit aorta. Eur. J. Pharmacol. **163:** 399–400, 1989.

SIM, M. K., AND MANJEET, S.: Properties of muscarinic receptors mediating second messenger responses in the rabbit aorta. Eur. J. Pharmacol. **189:** 399–404, 1990.

SIMMET, T., PRITZE, S., THELEN, K. I., AND PESKAR, B. A.: Release of endothelin in the oleic acid-induced respiratory distress syndrome in rats. Eur. J. Pharmacol. **211:** 319–322, 1992.

SIMONNEAU, G., ESCOURROU, P., DUROUX, P., AND LOCKHART, A.: Inhibition of hypoxic pulmonary vasoconstriction by nifedipne. N. Engl. J. Med. **304:** 1582–1885, 1981.

SMIRNOV, S. V., ROBERTSON, T. P., WARD, J. P. T., AND AARONSON, P. I.: Chronic hypoxia is associated with reduced delayed rectifier K^+ current in rat pulmonary artery muscle cells. Am. J. Physiol. **266:** H365–H370, 1994.

SOIFER, S. J., SCHREIBER, M. D., AND HEYMANN, M. A.: Leukotriene antagonists attenuate thromboxane-inducible pulmonary hypertension. Pediatr. Res. **26:** 83–87, 1989.

SOSTMAN, H. D., NEUMANN, R. D., GOTTSCHALK, A., AND GREENSPAN, R. H.: Perfusion of nonventilated lung: failure of hypoxic vasoconstriction? Am. J. Roentgenol. **141:** 151–156, 1983.

SPRAUGE, R. S., STEPHENSON, A. H., AND LONIGRO, A.: Prostaglandin I_2 supports blood flow to hypoxic alveoli in anesthetized dogs. J. Appl. Physiol. **56:** 1246–1251, 1984.

SPRAUGE, R. S., TJIEMERMANN, C., AND VANE, J. R.: Endogenous endothelium-derived relaxing factor opposes hypoxic pulmonary vasoconstriction and supports blood to hypoxic aiveoli in anesthetized rabbits. Proc. Natl. Acad. Sci. USA **89:** 8711–8715, 1992.

STAMLER, J. S., LOH, E., RODDY, M-A., CURRIE, K. E., AND CREAGER, M. A.: Nitric oxide regulates basal systemic and pulmonary vascular resistance in healthy humans. Circulation **89:** 2035–2040, 1994.

STAMLER, J. S., SINGEL, D. J., AND LOSCALZO, J.: Biochemistry of nitric oxide and its redox activated forms. Science (Wash. DC) **258:** 1898–1902, 1992.

STANBROOK, H. S., AND MCMURTRY, I. F.: Inhibition of glycolysis potentiates hypoxic vasoconstriction in rat lung. J. Appl. Physiol. **55:** 1467–1473, 1983.

STARKE, K., GOTHERT, M., AND KILBINGER, H.: Modulation of neurotransmitter release by presynaptic autoreceptors. Physiol. Rev. **69:** 864–989, 1989.

STEIN, M., AND LEVY, S. E.: Reflex and humoral responses to pulmonary embolism. Prog. Cardiovasc. Dis. **17:** 167–174, 1974.

STEINHORN, R., MORIN III, F. C., GUGINO, S. F., GIESE, E. C., AND RUSSELL, J. A.: Developmental differences in endothelium-dependent response in isolated ovine pulmonary arteries and veins. Am. J. Physiol. **264:** H2162–H2167, 1993.

STELZNER, T. J., O'BRIEN, R. F., YANAGISAWA, M., SAKURAI, M., SATO, K., WEBB, S., ZAMORA, M., MCMURTRY, I. F., AND FISHER, J. H.: Increase lung endothelin-1 production in rats with idiopathetic pulmonary hypertension. Am. J. Physiol. **262:** L614–L620, 1992.

STENMARK, K. R., ABMAN, S. H., AND ACCURSO, F. J.: Etiologic mechanisms in persistent pulmonary hypertension of the newborn. *In* Pulmonary Vascular Physiology and Pathophysiology, ed. by E. K. Weir and J. T. Reeves, pp. 355–402, Marcel Dekker, New York, 1989.

STEPHENSON, J. A., GIBSON, R. E., AND SUMMERS, R. J.: An autoradiographic study of muscarinic cholinoceptors in blood vessels: no localization on vascular endothelium. Eur. J. Pharmacol. **153:** 271–283, 1988.

STEPHENSON, J. A., AND SUMMERS, R. J.: Autoradiographic analysis of receptors on vascular endothelium. Eur. J. Pharmacol. **134:** 35–43, 1987.

STEVENS, T., JANSSEN, P. L., AND TUCKER, A.: Acute and long-term TNF-α administration increases pulmonary vascular reactivity in isolated rat lungs. J. Appl. Physiol. **73:** 708–712, 1992.

STEVENS, T., MORRIS, K., MCMURTRY, I. F., ZAMORA, M., AND TUCKER, A.: Pulmonary and systemic vascular responsiveness to TNF-α in conscious rats. J. Appl. Physiol. **74:** 1905–1910, 1993.

STEWART, D. J., LEVY, R. D., CERNACEK, P., AND LANGLEBEN, D.: Increased plasma endothelin-1 in pulmonary hypertension: marker or mediator of disease? Ann. Intern. Med. **114:** 464–469, 1991.

STEWART, A. G., SJEEDY, W., THOMPSON, J. S., AND MORICE, A. H.: Effects of SCH 34826, neutral endopeptidase inhibitor, on hypoxic pulmonary vascular remodelling. Pulm. Pharmacol. **5:** 111–114, 1992.

STOCLET, J-S., FLEMING, G., DRAY, G., JULON-SCHAEFFER, F., SCHNEIDER, C., SCHOTT, C., AND PARRAT, J. R.: Nitric oxide and endotoxemia. Circulation **87** (Suppl V)**:** V77–V80, 1993.

STRASSER, R., IHL-VAHL, R., AND MARQUETANT, R.: Molecular biology of adrenergic receptors. J. Hypertens. **10:** 501–506, 1992.

SUDJARWO, S. A., HORI, M., TAKAI, M., URADE, Y., OKADA, T., AND KARAKI, H.: A novel subtype od endothelin B receptor mediating contraction in swine pulmonary vein. Life Sci. **53:** 431–437, 1993.

SUDOH, T., KANGAWA, K., MINAMINO, N., AND MATSUO, H.: A new natriuretic peptide in porcine brain. Nature (Lond.) **332:** 78–81, 1988.

SUGA, S-I., NAKAO, K., ITOH, H., KOMATSU, Y., OGAWA, Y., HAMA, N., AND IMURA, H.: Endothelial production of C-type natriuretic peptide and its marked augmentation by transforming growth factor-β. J. Clin. Invest. **90:** 1145–1149, 1992.

SUMITA, T., ISHIKAWA, N., HASHIBA, Y., TAKAGI, K., AND SATAKE, T.: 5-Hydroxytryptamine receptor subtypes participating in pulmonary edema in dogs. Eur. J. Pharmacol. **164:** 69–75, 1989.

SUMMERS, R. J., MOLENAAR, P., STEPHENSON, J. A., AND JONES, C. R.: Autoradiographic localization of receptors in the mammalian cardiovascular system. Clin. Exp. Pharmacol. Physiol. **14:** 437–447, 1987.

SUNG, C. P., ARLETH, A. J., SHIKANO, K., AND BERKOWITZ, B. A.: Characterization and function of bradykinin receptors in vascular endothelial cells. J. Pharmacol. Exp. Ther. **247:** 8–13, 1988.

SZAREK, J. L., BAILLY, D. A., STEWART, N. L., AND GRUETTER, C. A.: Histamine H_1-receptors mediate endothelium-dependent relaxation of rat isolated pulmonary arteries. Pulm. Pharmacol. **5:** 67–74, 1992.

SZIDON, J. P., AND FISHMAN, A. P.: Participation of pulmonary circulation in the defence reaction. Am. J. Physiol. **220:** 364–370, 1981.

SZIDON, J. P., AND FLINT, J. F.: Significance of sympathetic innervation of pulmonary vessels in response to acute hypoxia. J. Appl. Physiol. **43:** 65–71, 1977.

TABRIZCHI, R., AND TRIGGLE, C. R.: Influence of N^W-nitro-L-arginine on pressor responses elecited by sympathetic nerve stimulation in pithed normotensive and hypertensive rats. Life Sci. **49:** 1989–1995, 1991.

TABUCHI, H., KAWAI, N., AND NAGASAKA, Y.: Favorable effect of long-term oxygen and vasodilator therapy in a patient with pulmonary hypertension associated with liver cirrhosis. Respir. Circ. **38:** 493–496, 1990.

TANAKA, D. T., AND GRUNSTEIN, M. M.: Vasoactive effects of substance P on isolated rabbit pulmonary artery. J. Appl. Physiol. **58:** 1291–1297, 1985.

TANAKA, H., BRADLEY, J. D., BAUDENDISTEL, L. J., AND DAHMS, T. E.: Mechanisms of pulmonary vsoconstriction induced by chemotactic peptide FMLP in isolated rabbit lungs. J. Appl. Physiol. **72:** 1549–1556, 1992.

TARE, M., PARKINGTON, H. C., COLEMAN, H. A., NEILD, T. O., AND DUSTING, G. J.: Hyperpolarization and relaxation of arterial smooth muscle caused by nitric oxide derived from the endothelium. Nature (Lond.) **346:** 69–71, 1990.

TAYLOR, I. M., AND SMITH, R. B.: Intrinsic innervation of the human foetal lung between the 35 and 140 mm crown-rump length stages. Biol. Neonate **18:** 193–202, 1971.

TESFAMARIAM, B., AND COHEN, R. A.: Inhibition of adrenergic vasoconstriction by endothelial cell shear stress. Circ. Res. **63:** 720–725, 1988.

THOMAS, H. M., AND GARRETT, R. C.: Strength of hypoxic vasoconstriction determines shunt fraction in dogs with atelectasis. J. Appl. Physiol. **53:** 44–51, 1982.

TIKTINSKY, M. H., AND MORIN, F. C.: Increased oxygen tension dilates fetal pulmonary circulation via endothelium-derived relaxing factor. Am. J. Physiol. **265:** H376–H380, 1993.

TIMMS, R. M., KHAJA, F. U., WILLIAMS, G.., AND NOCRURNAL OXYGEN THERAPY TRIAL GROUP: Hemodynamic response to oxygen therapy in chronic obstructive pulmonary disease. Ann. Intern. Med. **102:** 29–36, 1985.

TJEN-A-LOOI, S., EKMAN, R., LIPPTON, H., CARY, J., AND KEITH, I.: CGRP and somatostatin modulate chronic hypoxic pulmonary hypertension. Am. J. Physiol. **263:** H681–H690, 1992.

TOD, M. L., AND CASSIN, S.: Endothelin-1-induced pulmonary arterial dilation is reduced by N^w-nitro-L-arginine in fetal lambs. J. Appl. Physiol. **72:** 1730–1734, 1992.

TOD, M. L., CASSIN, S., MCNAMARA, D. B., AND KADOWITZ, P. J.: Effects of prostaglandin H_2 on perinatal pulmonary circulation. Pediatr. Res. **20:** 565–569, 1986.

TODA, N., AND OKAMURA, T.: Mechanism underlying the response to vasodilator nerve stimulation in isolated dog and monkey cerebral arteries. Am. J. Physiol. **259:** H1511–H1517, 1990.

TOGA, H., HIBLER, S., IBE, B. O., AND USHA RAJ, A.: Vascular effects of platelet-activating factor in lamb: role of cyco- and lipoxygenase. J. Appl. Physiol. **73:** 2599–2566, 1992a.

TOGA, H., IBE, B. O., AND USHA RAJ, J.: In vitro responses of ovine intrapulmonary arteries and veins to endothelin-1. Am. J. Physiol. **263:** L15–L21, 1992b.

TOGA, H., USHA RAJ, J., HILLYARD, R., KU., B., AND ANDERSON, J.: Endothelin effects in isolated, perfused lamb lungs: role of cyclooxygenase inhibition and vasomotor tone. Am. J. Physiol. **261:** H443–H450, 1991.

TRACEY, W. R., HAMILTON, J. T., CRAIG, I. D., AND PATERSON, N. A.: Effect of endothelial injury on the responses of isolated guinea pig pulmonary venules to reduced oxygen tension. Am. Rev. Respir. Dis. **140:** 68–74, 1989.

TSIEN, R. W., ELLINOR, P. T., AND HORNE, W. A.: Molecular diversity of voltage-dependent Ca^{2+} channels. Trends Pharmacol. Sci. **12:** 349–353, 1991.

TUCKER, A., MCMURTRY, I. F., GROVER, R. F., AND REEVES, J. T.: Attenuation of hypoxic pulmonary vasoconstriction by verapamil in intact dog. Proc. Soc. Exp. Biol. Med. **151:** 611–614, 1976a.

TUCKER, A., WEIR, E. K., REEVES, J. T., AND GROVER, R. F.: Pulmonary microembolism: attenuated pulmonary vasoconstriction with prostaglandin inhibitors and antihistamines. Prostaglandins **11:** 31–41, 1976b.

TUXEN, D. V., POWLES, A. C., MATHUR, P. N., PUGSLEY, S. O., AND CAMPBELL, E. J.: Detrimental effects of hydralazine in patients with chronic air-flow obstruction and pulmonary hypertension. A combined hemodynamic and radionuclide study. Am. Rev. Respir. Dis. **129:** 388–395, 1984.

UTSUNOMIYA, T., KRAUSZ, M. M., LEVINE, L., SHEPRO, D., AND HECHTMAN, H. B.: Thromboxane mediation of cardiopulmonary effects of embolism. J. Clin. Invest. **70:** 361–368, 1982.

UTSUNOMIYA, T., KRAUSZ, M. M., SHEPRO, D., AND HECHTMAN, H. B.: Prostaglandin control of plasma and platelet 5-hydroxytryptamine in normal and embolized animals. Am. J. Physiol. **241:** H766–H771, 1981.

VAN CHARLDORP, K. J. AND VAN ZWIETEN, P. A.: Comparison of the muscarinic receptors in the coronary artery, cerebral artery and atrium of the pig. Naunyn-Schmiedeberg's Arch. Pharmacol. **339:** 403–408, 1989.

VAN GELDEREN, E. M., DEN BOER, M. O., AND SAXENA, P. R.: N^G-nitro-L-arginine methyl ester: systemic and pulmonary haemodynamics, tissue blood flow and arteriovenous shunting in the pig. Naunyn-Schmiedeberg's Arch. Pharmacol. **348:** 417–423, 1993.

VANDONGEN, R.: Platelet activating factor and the circulation. J. Hypertens. **9:** 771–778, 1991.

VESTRI, R., PHILIP-JOET, F., SURPAS, P., ARNAUD, A., AND SAADJIAN, A.: One-year clinical study on nifedipine in the treatment of pulmonary hypertension in chronic obstructive lung disease. Respiration **54:** 139–144, 1988.

VOELKEL, N. F.: Mechanisms of hypoxic pulmonary vasococonstriction. Am. Rev. Respir. Dis. **133:** 1186–1195, 1986.

VOELKEL, N. F., GERBER, J. G., MCMURTRY, I. F., NIES, A. S., AND REEVES, J. T.: Release of vasodilator prostaglandin, PGI_2, from isolated rat lung during vasoconstriction. Circ. Res. **48:** 207–213, 1981.

VOELKEL, N. F., STENMARK, K. R., REEVES, J. T., MATHIAS, M. M., AND MURPHY, R. C.: Actions of lipoxygenase metabolites in isolated rat lungs. J. Appl. Physiol. **57:** 860–867, 1984.

VOELKEL, N. F., WORTHEN, S., REEVES, J. T., HENSON, P. M., AND MURPHY,

R. C.: Nonimmunological production of leukotrienes induced by platelet-activating factor. Science (Wash. DC) **218:** 286–288, 1982.

VOGAL, J. H. K., AND BLOUNT JR., S. G.: Role of beta adrenoceptors in the regulation of pulmonary circulation. (abstract) Circulation **32** (Suppl II): II-212, 1965.

VON EULER, U. S., AND LILJESTRAND, G.: Observations on the pulmonary arterial blood pressure in the cat. Acta Physiol. Scand. **12:** 301–320, 1947.

VON KUGELGEN, I. AND STARKE, K.: Noradrenaline-ATP co-transmission in the sympathetic nervous system. Trends Pharmacol. Sci. **12:** 319–324, 1991.

WALKER, B. R., HAYNES, J., JR., WANG, H. L., AND VOELKEL, N. F.: Vasopressin-induced pulmonary vasodilation in rats. Am. J. Physiol. **257:** H415–H422, 1989.

WANG, Q., AND LARGE, W. A.: Action of histamine on single smooth cells dispersed from the rabbit pulmonary artery. J. Physiol. (Lond.) **468:** 125–139, 1993.

WANG, X., HAN, C., AND FISCUS, R. R.: Calcitonin gene-related peptide (CGRP) cause endothelium-dependent cyclic AMP, cyclic GMP and vasorelant responses in art abdominal aorta. Neuropeptides **20:** 115–124, 1991.

WANSTALL, J. C., AND O'DONNELL, S. R.: Responses to vasodilator drugs on pulmonary artery preparations from pulmonary hypertensive rats. Br. J. Pharmacol. **105:** 152–158, 1992.

WARREN, J., MALTBY, N. H., MCCORMACK, D., AND BARNES, P. J.: Pulmonary endothelium derived relaxing factor is impaired by hypoxia. Clin. Sci. **77:** 671–676, 1989.

WIEBKE, J. L., MONTROSE-RAFIZADEH, C., ZEITLIN, P. L., AND GUGGINO, W. B.: Effect of hypoxia on endothelin-1 production by pulmonary vascular endothelial cells. Biochim. Biophys. Acta **1134:** 105–111, 1992.

WEIR, E. K.: Does normoxic pulmonary vasodilatation rather than hypoxic vasoconstriction account for the pulmonary pressor response to hypoxia? Lancet **1:** 476–477, 1978.

WEIR, E. K., MCMURTRY, I. F., TUCKER, A., REEVES, J. T., AND GROVER, R. F.: Prostaglandin synthetase inhibitors do not decrease hypoxic pulmonary vasoconstriction. J. Appl. Physiol. **41:** 714–718, 1976.

WEITZBERG, E., RUDEHILL, A., AND LUNDBERG, J. M.: Nitric oxide inhalation attenuates pulmonary hypertension and improves gas exchange in endotoxin shock. Eur. J. Pharmacol. **233:** 85–94, 1993.

WEITZENBLUM, E., OSWALD, M., MIRHOM, R., KESSLER, R., AND APPRILL, M.: Evolution of pulmonary haemodynamics in COLD patients under long-term oxygen therapy. Eur. Respir. J. **7** (suppl.)**:** 669 s–673 s, 1989.

WEITZENBLUM, E., SAUTEGEAU, A., EHRHART, M., MAMMOSSER, M., AND PELLETIER, A.: Long-term oxygen therapy can reverse the progression of pulmonary hypertension in patients with chronic obstructive pulmonary disease. Am. Rev. Respir. Dis. **131:** 493–498, 1985.

WEITZENBLUM, E., SCHRIJEN, F., MOHAN-KUMAR, T., COLAS DES FRANCS, V., AND LOCKHART, A.: Variability of the pulmonary vascular response to acute hypoxia in chronic bronchitis. Chest **94:** 772–778, 1988.

WINK, D. A., KASPRZAK, K. S., AND MARANGOS, C. M.: DNA deaminating ability and genotoxicity of nitric oxide and its progenitors. Science (Wash. DC) **259:** 1000–1003, 1991.

WESTENDORP, R. G. J., ROOS, R. N., VD. HOEVEN, H. G., TJIONG, M. Y., SIMONS, R., FROLICH, M., SOUVERIJN, J. H. M., AND EDO MEINDERS, A.: Atrial natriuretic peptide improves pulmonary gas exchange in subjects exposed to hypoxia. Am. Rev. Respir. Dis. **148:** 304–309, 1993.

WHEELER, A. P., HARDIE, W. D., AND BERNARD, G. R.: The role of cyclooxygenase products in lung injury induced by tumor necrosis factor in sheep. Am. Rev. Respir. Dis. **145:** 632–639, 1992.

WICKS, T. C., ROSE, J. C., JOHNSON, M., RAMWELL, P. W., AND KOT, P. A.: Vascular responses to arachidonic acid in the perfused canine lung. Circ. Res. **38:** 167–171, 1976.

WIEBKE, J. L., MONTROSE-RAFIZADEH, C., ZEITLIN, P. L., AND GUGGINO, W. B.: Effect of hypoxia on endothelin-1 production by pulmonary vascular endothelial cells. Biochim. Biophys. Acta **1134:** 105–111, 1992.

WIENER, C. M., DUNN, A., AND SYLVESTER, J. T.: ATP-dependent K^+ channels modulate vasoconstrictor responses to severe hypoxia in isolated ferret lungs. J. Clin. Invest. **88:** 500–504, 1991.

WIKLUND, N. P., CEDERQVIST, B., AND GUSTAFSSON, L. E.: Adenosine enhancement of adrenergic neuroeffector transmission in guinea-pig pulmonary artery. Br. J. Pharmacol. **96:** 425–433, 1989a.

WIKLUND, N. P., OHLEN, A., AND CEDERQVIST, B.: Adrenergic neuromodulation by endothelin in guinea pig pulmonary artery. Neurosci. Lett. **101:** 269–273, 1989b.

WIKLUND, N. P., PERSSON, M. G., GUSTAFSSON, L. E., MONCADA, S., AND HEDQVIST, P.: Modulatory role of endogenous nitric oxide in pulmonary circulation in vivo. Eur. J. Pharmacol. **185:** 123–124, 1990.

WILKINSON, M., LANGHORNE, C. A., HEATH, D., BARER, G. R., AND HOWARD, P.: A pathophysiological study of 10 cases of hypoxic cor pulmonale. Q. J. Med. **66:** 65–85, 1988.

WILSON, L. B., AND LEVITZKY, M. G.: Chemoreflex blunting of hypoxic pulmonary vasoconstriction is vagally mediated. J. Appl. Physiol. **66:** 782–791, 1989.

WIMMER, M., SCHLEMMER, M., AND EBNER, F.: Hemodynamic effects of nifedipine and oxygen in children with pulmonary hypertension. Cardiovasc. Drugs Ther. **2:** 661–668, 1988.

WINTER, R. J. D., DAVIDSON, A. C., TREACHER, D., RUDD, R. M., ANDERSON, J. V., MELEAGROS, L., AND BLOOM, S. R.: Atrial natriuretic peptide concentrations in hypoxic secondarry pulmonary hypertension: relation to haemodynamic and blood gas variables and response to supplemental oxygen. Thorax **44:** 58–62, 1989.

WONG, J., VANDERFORD, P. A., FINEMAN, J. R., CHANG, R., AND SOIFER, S. J.: Endothelin-1 produces pulmonary vasodilation in the intact newborn lamb. Am. J. Physiol. **265:** H1318–H1325, 1993.

WORTHEN, G. S., GUMBAY, R. S., TANAKA, D. T., AND GRUNSTEIN, M. M.: Opposing hemodynamic effects of substance P on pulmonary vasculature in rabbits. J. Appl. Physiol. **59:** 1098–1103, 1985.

WRIGHT, J. L., PETTY, T., AND THURLBECK, W. M.: Analysis of the structure of the muscular pulmonary arteries in patients with pulmonary hypertension and COPD: National Institutes of Health nocturnal oxygen therapy trial. Lung **170:** 109–124, 1992.

XIE, J., WANG, Y., LIPPTON, H., CAI, B., NELSON, S., KOLLS, J., SUMMER, W. R., AND GREENBERG, S. S.: Tumor necrosis factor inhibits stimulated but not basal release of nitric oxide. Am. Rev. Respir. Dis. **148:** 627–636, 1993.

YAMAGUCHI, T., RODMAN, D., O'BRIEN, R., AND MCMURTRY, I. F.: Modulation of pulmonary artery contraction by endothelium-derived relaxing factor. Eur. J. Pharmacol. **161:** 259–262, 1989.

YAMAMOTO, R., WADA, A., ASADA, Y., NIINA, H., AND SUMIYOSHI, A.: N^W-nitro-L-arginine, an inhibitor of nitric oxide synthesis, decreases noradrenaline outflow in rat isolated perfused mesenteric vasculature. Naunyn-Schmiedeberg's Arch. Pharmacol. **347:** 238–240, 1993.

YAMANAKA, S., MIURA, K., YUKIMURA, T., OKUMURA, M., AND YAMAMOTO, K.: Putative mechanism of hypotensive action of platelet-activating factor in dogs. Circ. Res. **70:** 893–901, 1992.

YOKOKAWA, K., TAHARA, H., KOHNO, M., MANDAL, A. K., YANAGISAWA, M., AND TAKEDA, T.: Heparin regulates endothelin production through endothelium-derived nitric oxide in human endothelial cells. J. Clin. Invest. **92:** 2080–2085, 1993.

YOSHIBAYASHI, M., NISHIOKA, K., NAKAO, K., SAITO, Y., MATSUMURA, M., UEDA, T., TEMMA, S., SHIRAKAMI, G., IMURA, H., AND MIKAWA, H.: Plasma endothelin concentrations in patients with pulmonary hypertension associated with congenital heart defects. Evidence for increased production of endothelin in pulmonary circulation. Circulation **84:** 2280–2285, 1991.

YOSHIZUMI, M., PERELLA, M. A., BURNETT, J. C. J., AND LEE, M-E.: Tumor necrosis factor downregulates an endothelial nitric oxide synthase mRNA by shortening its half life. Circ. Res. **73:** 205–209, 1993.

YOUNG, T. E., LUNDQUIST, L. J., CHESLER, C., AND WEIR, E. K.: Comparative effects of nifedipine, verapamil, diltiazem on experimental pulmonary hypertension. Am. J. Cardiol. **51:** 195–200, 1983.

YUAN, X-J., GOLDMAN, W. F., TOD, M. L., RUBIN, L. J., AND BLAUSTEIN, M. P.: Ionic currents in rat pulmonary and mesenteric arterial myocytes in primary culture and subculture. Am. J. Physiol. **264:** L107–L115, 1993a.

YUAN, X-J., GOLDMAN, W. F., TOD, M. L., RUBIN, L. J., AND BLAUSTEIN, M. P.: Hypoxic reduces potassium currents in cultured rat pulmonary but not mesenteric arterial myocytes. Am. J. Physiol. **264:** L116–L123, 1993b.

YUAN, Y., GRANGER, H. J., ZAWIEJA, D. C., DEFILY, D. V., AND CHILIAN, W. M.: Histamine increases venular permeability via a phospholipase C-NO synthase-guanylate cyclase cascade. Am. J. Physiol. **264:** H1734–H1739, 1993c.

ZAMORA, C. A., BARON, D. A., AND HEFFNER, J. E.: Thromboxane contributes to pulmonary hypertension in ischemia-reperfusion lung injury. J. Appl. Physiol. **74:** 224–229, 1993a.

ZAMORA, M., DEMPSEY, E. C., WALCHAK, S. J., AND STELZER, T. J.: BQ123, an ET_A receptor antagonist, inhibits endothelin-1-mediated proliferation of human pulmonary artery smooth muscle cells. Am. J. Respir. Cell Mol. Biol. **9:** 429–433, 1993b.

ZELLERS, T. M., AND VANHOUTTE, P. M.: Endothelium-dependent relaxations of piglet pulmonary arteries augment with maturation. Pediatr. Res. **30:** 176–180, 1991.

ZHAO, L., CRAWLEY, D. E., HUGHES, J. M., EVANS, T. W., AND WINTER, R. J.: Endothelium-derived relaxing factor activity in rat lung during hypoxic pulmonary vascular remodeling. J. Appl. Physiol. **74:** 1061–1065, 1993.

ZHAO, L., WINTER, R. J., KRAUSZ, T., AND HUGHES, J. M.: Effects of continuous infusion of atrial natriuretic peptide on the pulmonary hypertension induced by chronic hypoxia in rats. Clin. Sci. **81:** 379–385, 1991.

ZHOU, Q-Y., LI., C., OLAH, M., JOHNSON, R. A., STILES, G. L., AND CIVELLI, O.: Molecular cloning and characterization of an adenosine receptor: the A_3-adenosine receptor. Proc. Natl. Acad. Sci. USA **89:** 7432–7436, 1992.

ZUBROW, A. B., IMAIZUMI, S. O., AND TULENKO, T. N.: Endothelium-mediated relaxation in the fetal pulmonary artery. (abstract) Pediatr. Res. **25:** 75A, 1989.