

Role of serotonin in the pathogenesis of acute and chronic pulmonary hypertension

Paul Egermayer, G Ian Town, Andrew J Peacock

The causes of pulmonary hypertension fall into four broad categories: (1) passive increases in pulmonary artery pressure secondary to increased left atrial pressure and left ventricular dysfunction, (2) veno-occlusive disorders, (3) conditions in which the blood flow through the pulmonary arteries is increased beyond the ability of the pulmonary circulation to compensate, and (4) conditions associated with vasospasm or occlusion, resulting in a diminished effective cross sectional area of the pulmonary vascular bed.^{1,2} In many cases several factors are present simultaneously. Regardless of the initiating cause, severe prolonged pulmonary hypertension appears to result in largely irreversible changes which involve vascular remodelling and often thrombosis.³⁻⁵

Because the signs and symptoms of pulmonary hypertension are often very non-specific, patients commonly present late and, until recently, invasive tests were required to establish the diagnosis. Consequently pulmonary hypertension was frequently an important but unrecognised component of other disease states, many of which will be the subject of this discussion.

The main importance of severe pulmonary hypertension is that it may cause right ventricular dysfunction and ultimately death from right heart failure. Pulmonary heart disease, usually associated with pulmonary hypertension, has been estimated to account for at least 10% of all cases of heart disease in the USA.⁶ The significance of milder pulmonary hypertension is less clear, but it is probably important. A study in Chicago of 1118 subjects who were undergoing coronary angiography for suspected heart disease showed that the finding of pulmonary hypertension, independent of left ventricular dysfunction, was the single most important predictor of the likelihood of death over the subsequent two years.⁷ Pulmonary hypertension also has important prognostic implications in critically ill surgical patients⁸ and in those with chronic obstructive pulmonary disease (COPD).⁹

The changes which take place in pulmonary arteries as a result of hypertension have been intensively studied, and numerous pro-inflammatory factors have been identified which can influence these changes.¹⁰ It is often difficult, if not impossible, to distinguish cause from effect. However some factors are frequently present. The aim of the present discussion is to examine the possible role of one such factor, serotonin. This may have added importance since a number of serotonin antagonists are available for oral use. For the

purposes of this review pulmonary hypertension is defined as a pulmonary artery pressure of >25 mm Hg at rest.

Origin of serotonin and causes of elevated levels

Serotonin, also known as 5-hydroxytryptamine, is secreted from neuroendocrine cells in the gut, and tumours of these cells, called carcinoid tumours, are a source of increased production.^{11,12} Serotonin from the gastrointestinal tract is normally metabolised by the liver before it reaches the lungs, and it is also effectively removed by the lungs. Both these organs usually localise the effects of serotonin to the circulation of origin, except when abnormal channels of communication exist, as in portal hypertension, or when metabolic capacity is overwhelmed. Lack of removal of vasoactive substances by the liver could help to explain the association between pulmonary hypertension, portal hypertension, and liver diseases.^{13,14} The vascular adverse effects of serotonergic amines such as ergotamine are exacerbated in liver disease.¹⁵ The ability of the endothelial cells of the lungs to metabolise amines may also be reduced in disease states, probably because of impairment of amine oxidase enzymes.^{16,17} Such impairment results in raised circulating amine levels, which may provide early evidence of endothelial dysfunction in pulmonary hypertension before morphological changes are apparent.^{18,19}

Pulmonary neuroendocrine cells secrete vasoactive substances in response to airway hypoxia and hypercapnia.^{20,21} For unknown reasons these cells commonly proliferate in patients with pulmonary hypertension, producing a variety of peptides in addition to large amounts of serotonin.²² In lung transplant recipients with end stage primary pulmonary hypertension the degree of hyperplasia of these cells was found to correlate with the extent of proliferation of myofibroblasts in the pulmonary arteries.²³ In bronchopulmonary dysplasia, a condition strongly associated with pulmonary hypertension, a 34-fold increase in serotonin immunoreactive cells has been demonstrated.²⁰ Pulmonary neuroendocrine cells, rather than platelets, have been postulated to be the source of increased serotonin production causing acute postoperative pulmonary hypertension in children with congenital heart defects.^{24,25} The mast cell also contributes to increased levels of circulating serotonin in the pulmonary hypertension which occurs in rats following exposure to asbestos.²⁶

Conditions associated with the destruction of platelets are likely to cause the release of serotonin and other contents which may cause

Canterbury
Respiratory Research
Group, Christchurch
School of Medicine,
Christchurch,
New Zealand
P Egermayer
G I Town

Department of
Respiratory Medicine,
Western Infirmary,
Glasgow G11 6NT, UK
A J Peacock

Correspondence to:
Dr G I Town, Christchurch
School of Medicine, P O Box
4345, Christchurch,
New Zealand.

Received 9 February 1998
Returned to author
8 May 1998
Revised manuscript received
15 June 1998
Accepted for publication
11 September 1998

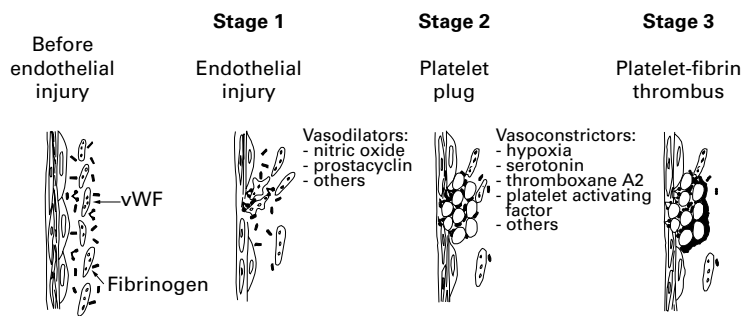


Figure 1 Stages in the interaction of platelets with the walls of pulmonary arteries following trauma. Stage 1: adhesion of platelets following endothelial injury mediated by von Willebrand factor (vWF). Stage 2: formation of the platelet plug with aggregation and degranulation (some of the most important vasoconstricting and vasodilating substances are listed, many of which are released from platelets). Stage 3: fibrin clot formation (mediated by fibrinogen). Modified from reference 186 with permission.

pulmonary hypertension.²⁷ Immune mediated acute thrombocytopenia is one such condition.²⁸ The aggregation of platelets also releases serotonin, and when the process occurs in pulmonary arteries this causes vasospasm.²⁹ Binding of platelets to arteries is mediated largely by von Willebrand factor and factor VIII.³⁰ Increased aggregation of platelets and decreased platelet survival time are regularly observed in most forms of primary and secondary pulmonary hypertension.^{4 31} Abnormalities of endothelial factor VIII have been observed in cases of pulmonary hypertension in both humans and sheep,³²⁻³⁴ and adherence of platelets to the pulmonary arteries in pulmonary hypertension is likely to be pathologically enhanced by the increases in endothelial von Willebrand factor which result from increased shear stress (fig 1).³⁵ These changes may lead to pulmonary arteriosclerosis, which is usual in pulmonary hypertension.³⁶

Circulating serotonin is taken up by endothelial cells, and even more so by platelets, where it is stored in dense (delta) granules.³⁰ When the endothelial cells or platelets are unable to take up serotonin because of damage or as a result of congenital abnormalities, circulating serotonin levels are increased and pulmonary hypertension may result. The increases in serotonin levels in patients with these problems persist following normalisation of pulmonary artery pressures after lung transplantation, indicating that the platelet abnormality is not caused by pulmonary hypertension.³⁷

Effects of serotonin

A number of biogenic and synthetic amines are capable of causing endothelial disruption and platelet stimulation. Serotonin is somewhat unique in that these changes occur at levels which are not much higher than the "resting levels" which are observed in mammalian blood.³⁸ The opening of junctions between endothelial cells causes oedema.³⁹ On a molar basis, serotonin is the most potent pulmonary vasoconstrictor identified to date in humans,⁴⁰ but in the systemic vasculature it causes profound vasodilation.⁴¹ These differing effects on the two circulations are similar to those of hypoxaemia and the effects of serotonin are intensified under hypoxaemic conditions and

by the administration of catecholamines.⁴¹ In conditions characterised by stimulation of the sympathetic nervous system, such as cardiopulmonary bypass, subthreshold doses of serotonin can have significant vasoconstrictor effects.⁴² The vasoconstrictor effects of serotonin have been found to be synergistic with other concomitant variables which are too numerous to list.⁴³ Serotonin is also a bronchoconstrictor.^{41 44}

Serotonin is a mitogen, causing hyperplastic and hypertrophic changes in smooth muscles.⁴⁵ The most readily identifiable clinical manifestation of this effect is valvular heart disease.⁴⁶ These effects are mediated by a variety of cellular processes, including cyclic nucleotides and protein kinase C activation.^{47 48} A complex interplay exists at a systemic and local level between inflammation, thrombosis, fibrinolysis, vasospasm, and vascular remodelling. Many of the important mitogens implicated in remodelling have a vasoconstrictor and prothrombotic effect, and vasodilators such as nitric oxide inhibit platelet aggregation, thrombosis, and remodelling.⁴⁹ The histological changes which occur during pulmonary vascular remodelling have been reviewed elsewhere.³⁻⁵ Remodelling has many features in common with the changes that occur in arteriosclerosis, except that arteriosclerosis generally involves larger vessels with a high elastin content.⁵⁰ Endothelial proliferation may also be more exuberant in some varieties of pulmonary hypertension than in arteriosclerosis.³² Hypoxia and stretching of the pulmonary vessels are believed to be important stimuli for these processes which involve phenotypic changes in endothelial cells, myofibroblasts, and numerous types of inflammatory cells.^{51 52} The end result of these changes are structural and functional changes which result in an increased pulmonary vascular resistance. These changes were accelerated by the administration of serotonin to rats exposed to chronic hypoxia.^{53 54}

Serotonin receptors

At least five classes of serotonin receptor have been identified, each with numerous subclasses, and different receptors have been implicated in the pathogenesis of a number of vascular disorders.⁵⁵ S₁ and S₂ are the principal receptors relevant to the pulmonary arteries.⁵⁶ The vascular response to serotonin is determined by a large number of concomitant variables, and also varies between vasodilation and vasoconstriction in different segments of the same artery, which makes generalisation difficult.⁵⁷ However, under most experimental conditions, stimulation of S₁ pulmonary receptors causes vasodilation and S₂ receptors often mediate vasospasm.⁵⁶ Functional imbalance of this system may result in hypertension, as in pre-eclampsia.⁵⁸ With arteriosclerosis, numbers of S₂ receptors are increased, causing increased sensitivity to serotonin.⁵⁹⁻⁶¹ Arteriosclerosis also appears to predispose to vasospasm due to deficiencies of endothelial vasodilation.⁶²

Serotonergic agents

Pulmonary hypertension can be caused in most mammalian species by numerous serotonergic drugs, many of which are sympathomimetic anorexients. These include aminorex⁶³ and dexfenfluramine.⁶⁴ In rabbits, aminorex and other anorexients cause release of serotonin from platelets.⁶⁵ In dogs, intravenous dexfenfluramine augments hypoxic pulmonary vasoconstriction and, with long term oral use, pulmonary vascular resistance is increased.⁶⁶ In rats phentermine and phenmetrazine cause pulmonary vasoconstriction by prolonging the vasoconstrictive influence of serotonin.^{67,68} More recently three other anorexient agents were found to cause pulmonary vasoconstriction by inhibiting potassium current in pulmonary vascular smooth muscle, an action which mimicked the effect of hypoxia.⁶⁹ Other drugs with direct or indirect serotonergic effects⁷⁰ have been associated with pulmonary hypertension—namely, cocaine,⁷¹ dopamine,⁷² doxapram,⁷³ fluoxetine,⁷⁴ lithium,⁷⁵ methamphetamine,⁷⁶ methysergide,⁷⁷ pentazocine,⁷⁸ phenmetrazine,⁷³ protamine,⁷⁹ sertaline,⁸⁰ and tryptophan.⁸¹ Most of these reactions are infrequent, implying individual variations in susceptibility, and for several of these agents possible alternative mechanisms of toxicity exist, but the common feature of serotonergy suggests that these may often be synergistic. In the case of pentazocine, for example, there are numerous reports concerning the illicit intravenous use of tablets containing talc, which cause a granulomatous arteritis, frequently resulting in chronic pulmonary hypertension. Crushed pentazocine tablets injected into dogs also cause transient pulmonary hypertension.⁸² However, other more common illicit drugs which are used in a similar way appear to cause these problems less frequently,⁸³ and acute pulmonary hypertension is also a well established effect of pure pentazocine.

The pulmonary vasodilator urapidil is primarily an alpha-1 adrenoreceptor blocker, but may also act by stimulating S₁ receptors.⁸⁴

Specific pulmonary hypertensive diseases which may involve serotonin

THE CARCINOID SYNDROME

Investigators have found that about 25% of patients with the carcinoid syndrome have pulmonary hypertension which is often relatively mild.⁸⁵ This is probably because of liver metabolism, since liver dysfunction is a prerequisite for the production of cardiac lesions in the guinea pig model of this disease.⁸⁶ In addition to valve disease, pulmonary hypertension may contribute to the commonly observed tricuspid regurgitation.⁸⁷ More severe valvular disease is found in patients with higher serotonin levels.^{88,89} Similar valvular lesions have frequently been observed during the use of ergotamine and methysergide, both of which are partial serotonin agonists, and have recently been reported in association with diet pills which also have serotonergic properties.⁹⁰ Carcinoid tumours secrete peptides which also characteristically provoke florid vascular fibro-

proliferative reactions.^{91,92} Ketanserin provides relief of many of the symptoms of the carcinoid syndrome and, when used during anaesthesia, consistently reverses systemic hypertension,⁴³ but the effects on pulmonary hypertension have not been studied.

MONOCROTALINE INDUCED PULMONARY HYPERTENSION

The plant *Crotalaria spectabilis* (the source of monocrotaline) is often used to induce pulmonary hypertension in experimental animals, most commonly the rat, and also has this effect in man. Endothelial injury is the first change observed, followed by hypertrophy of arterial smooth muscle and right ventricular hypertrophy.^{93,94} Plasma serotonin levels are increased, coinciding with platelet accumulation in the lungs, the vasoconstrictor response to serotonin is enhanced, and both pulmonary artery pressure and the severity of histological changes are reduced by selective serotonin blockade and by inhibition of serotonin synthesis with chlorophenylalanine.^{95,96} The hypertensive effect of monocrotaline was reduced in rats made moderately thrombocytopenic with antiplatelet serum,⁹⁷ and by the platelet modifying drug sulphinpyrazone.⁹⁸ Prednisolone was also beneficial.⁹⁹ However, the thromboxane inhibitor dazmegrel was ineffective, suggesting a less important role for thromboxane A₂ in this disorder.¹⁰⁰

PULMONARY EMBOLISM

The pulmonary hypertension associated with acute pulmonary embolism (PE) is sometimes disproportionate to the degree of physical vascular occlusion, and some of this has been attributed to the vasoconstrictive effects of platelet derived serotonin.¹⁰¹⁻¹⁰³ Bronchoconstriction following PE may have the same cause.^{104,105} Platelets adhere to the thrombus which has lodged in the pulmonary arteries^{106,107} and this commonly results in depletion of circulating platelet levels.¹⁰⁸ Experimental embolisation in animals with fresh thrombotic material containing large amounts of platelet derived serotonin generates a more profound pulmonary vasoconstrictor response than embolisation with barium, glass beads, and other objects which do not contain platelets or stimulate thrombin mediated platelet degranulation.^{41,109} The degree of vasoconstriction is also proportionate to the extent of endothelial damage caused by the embolus.¹¹⁰ If experimental animals are rendered thrombocytopenic prior to embolisation, the pulmonary hypertension is significantly attenuated and inhibition of the platelet release reaction with sulphinpyrazone or heparin has a similar effect.^{111,112} A significant average reduction of approximately 5 mm Hg in the pulmonary hypertension generated by PE was observed in humans after the administration of ketanserin.¹¹³ Ketanserin and other serotonin blockers also reduce post embolic pulmonary hypertension in dogs.^{112,114}

RADIATION PNEUMONITIS AND ANTITUMOUR DRUGS

Irradiation of tissues causes release of serotonin as evidenced by direct measurement,¹¹⁵ and indirectly by the well established beneficial effects of S_2 receptor antagonists in the treatment of radiation induced side effects.¹¹⁶ Endothelium is a rapidly dividing tissue which suffers the early effects of radiation,¹¹⁷ and pulmonary hypertension often results.^{118 119} Serotonin levels were also increased significantly following treatment with vinblastine and other antitumour drugs.¹²⁰

ADULT RESPIRATORY DISTRESS SYNDROME AND SHOCK

Pulmonary hypertension is observed in almost all cases of adult respiratory distress syndrome (ARDS),⁴⁰ and vascular remodelling is pronounced in patients who survive longer than 10 days.¹²¹ Progressive thrombocytopenia occurs in 50% of cases, and often parallels the course of worsening hypoxia.^{122 123} Platelet activation and intrapulmonary platelet aggregation are also common.^{124 125} Sibbald *et al* observed a correlation between raised serotonin levels and pulmonary hypertension in patients with ARDS related to sepsis.¹²⁶ Serotonin contributed to pulmonary hypertension in dogs during haemorrhagic shock, and this hypertension was prevented with serotonin antagonists.¹²⁷ Administration of ketanserin to patients with acute respiratory failure following circulatory shock also caused significant haemodynamic improvements.¹²⁸

COLLAGEN DISORDERS

Pulmonary hypertension is a complication of most varieties of collagen disease, particularly systemic lupus erythematosus (SLE), a disease in which pulmonary artery pressures were raised in over 30% of consecutive cases in several series.¹²⁹⁻¹³¹ Patients with SLE and Raynaud's syndrome appear to be particularly susceptible.¹³² Intraplatelet and circulating serotonin levels were found to be significantly higher in patients with calcinosis, Raynaud's phenomenon, and oesophageal dysmotility (the CREST variant) than in controls.^{133 134} Stachow *et al* found evidence of impaired monoamine oxidase activity in scleroderma, and the increased levels of serotonin observed were normalised by treatment with ketanserin.¹³⁵ In a multicentre trial oral ketanserin reduced the frequency of episodes of Raynaud's symptoms from 34% to 18% among 222 patients⁴³ and, in a study of 14 patients with systemic sclerosis and relatively severe pulmonary hypertension, Seibold *et al* found that intravenous ketanserin decreased pulmonary artery pressure by 13-44% in five patients but caused a paradoxical increase in one, with no change in the other eight.¹³⁶

PORTAL HYPERTENSION

Hadengue *et al* found that 2% of 507 patients with portal hypertension also had pulmonary hypertension and the portal hypertension usually preceded the pulmonary hypertension.¹³⁷ These authors postulated that either microem-

boli or unspecified vasoactive substances were bypassing the liver to reach the lung by way of portosystemic shunts. Thrombocytopenia was present in most cases of portal hypertension with plexogenic pulmonary arteriopathy.¹³⁸

HYPOXIC DISORDERS

Because of the prevalence of chronic lung disease, hypoxia is probably the commonest of all causes of pulmonary hypertension apart from diseases caused by parasites.² The mechanisms of hypoxic vasoconstriction have been reviewed elsewhere, but much remains unknown.¹³⁹ Hypoxia complicates many of the other diseases which have already been discussed, and modifies the effects of many vasoactive substances.^{140 141} In healthy subjects hypoxia per se does not appear to increase circulating serotonin levels,¹⁴² but levels are increased in patients with several types of chronic lung disease and associated pulmonary hypertension.^{143 144} Patients with chronic obstructive pulmonary disease (COPD) and pulmonary hypertension show evidence of greater activation of platelets in pulmonary vessels than those with normotensive COPD,^{145 146} and a reduced platelet survival time is also found.¹⁴⁷ In animal models platelets release their contents into the lung during hypoxic vasoconstriction.¹⁴⁸ The release of platelet contents and the progression of pulmonary hypertension in patients with COPD may be slowed with the use of the platelet-inhibiting drug dipyridamole.^{149 150} This agent also reduced pulmonary artery pressure and the thickness of pulmonary arteries in rats exposed to chronic hypoxia.^{151 152}

Inherited and acquired platelet disorders

PLATELET STORAGE POOL DISEASES

As noted above, patients with a deficiency of dense granules in platelets are unable to take up serotonin from the blood, often resulting in increased circulating levels of the amine. One such case of "platelet storage pool disease" has been described in which the patient developed severe pulmonary hypertension long after the platelet disorder was diagnosed.¹⁵³ Ketanserin alleviated the pulmonary hypertension in this case. An experimental model of platelet storage pool disease exists in the fawn hooded rat, an animal which is studied for its propensity to develop pulmonary hypertension.¹⁵⁴ In this species pulmonary vascular smooth muscle proliferates more rapidly in response to epidermal growth factor than in normotensive rats,¹⁵⁵ there is increased vasoconstrictor sensitivity to serotonin,¹⁵⁶ and decreased biogenic amine removal by lung tissue.¹⁵⁷ These rats also appear to have a genetic propensity to overproduce endothelin-1, another mitogen and vasoconstrictor.¹⁵⁸

An acquired form of platelet storage pool disease, associated with disordered uptake of serotonin, occurs commonly in patients with myeloproliferative disorders.¹⁵⁹ Portal hypertension is a well recognised complication of these disorders and, in one series, a 13% incidence of pulmonary hypertension was also observed.¹⁶⁰ Platelets in patients with

myeloproliferative disorders have also been found to have a selectively exaggerated serotonin release induced by immune complexes.¹⁶¹

PLATELET CELL MEMBRANE DISORDERS

In addition to myeloproliferative disorders, other diseases are characterised by platelet cell membrane abnormalities, thrombocytopenia, increased circulating serotonin levels, portal hypertension, and pulmonary hypertension. These include paroxysmal nocturnal haemoglobinuria¹⁶²⁻¹⁶⁴ and the antiphospholipid syndrome.

Antiphospholipid antibodies occur in about 10% of patients with chronic thromboembolic pulmonary hypertension.¹⁶⁵ Other pulmonary manifestations include: (1) pulmonary emboli, (2) adult respiratory distress syndrome, (3) alveolar haemorrhage, (4) pulmonary capillaritis, and (5) primary thrombosis of the lung vessels.¹⁶⁶ These antibodies are also commonly found in association with collagen diseases. They may interact with phospholipids and phospholipid-bound proteins in blood vessel walls and platelets causing damage to vessel walls and platelet aggregation, resulting in thrombocytopenia.^{167 168}

THROMBOCYTOPENIA IN PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN

Platelets have been also implicated in the pathophysiology of persistent pulmonary hypertension of the newborn. Segall *et al* identified 90 newborn infants with perinatal asphyxiation and found that only the 12 infants with thrombocytopenia had proven pulmonary hypertension.¹⁶⁹ These authors suspected that platelet derived thromboxane A₂ may have caused the hypertension, but were unable to find a correlation between pulmonary artery pressures and prostaglandin metabolites. In another study it was determined prospectively that infants who developed persistent pulmonary hypertension as a result of meconium aspiration could be identified by the onset of thrombocytopenia prior to the hypertension.¹⁷⁰

Serotonin antagonists

The S₂ receptor antagonist ketanserin is the best studied agent of this type for reducing pulmonary hypertension or vascular resistance. Inhibition of platelet aggregation is another effect.⁴³ Like most vasodilators this drug has varying efficacy, reflecting the complex pathophysiology of the disease. In the treatment of primary pulmonary hypertension, McGoon *et al* detected an average reduction of pulmonary vascular resistance of 18% with intravenous use in 10 patients.¹⁷¹ In a later study of 20 patients, eight of whom had not previously responded to other vasodilator therapy, the same authors found a small but significant decrease in pulmonary vascular resistance in the group as a whole, with a clinically significant response in three patients.¹⁷² In addition to conditions previously discussed, studies showing haemodynamic benefits with ketanserin have involved patients with protamine induced pulmonary hypertension,⁷⁹ respiratory failure,¹²⁸ and valve surgery.^{173 174} In comparison to nitroprusside,

ketanserin usually improved gas exchange.¹⁷⁵ However Hamet *et al* could detect no change following administration of ketanserin in patients with hypoxic COPD.¹⁷⁶ Animal studies involving different species have shown decreases in pulmonary artery pressure following pulmonary oedema after acid injury,¹⁷⁷ serotonin induced pulmonary hypertension,¹⁷⁸ and endotoxaemia.¹⁷⁹ In the latter condition there is a phasic response. In several species serotonin was found to mediate the pulmonary hypertension occurring three hours after endotoxin injections, but not the more severe pulmonary hypertension which occurred earlier. Ketanserin had no effect in the first two hours, but was effective after three hours at a time when platelet counts ceased to fall.¹⁸⁰⁻¹⁸² Droperidol has been observed to prevent serotonin-induced bronchospasm and pulmonary hypertension in humans and dogs.^{183 184}

Numerous pulmonary vasodilators are available, but their influence on survival has not been adequately demonstrated. Ketanserin is seldom mentioned in reviews of these agents, although in the short term it appears to be as efficacious as many other agents that have been more extensively studied. The effects of ketanserin on pulmonary hypertension suggest that serotonergic mechanisms may be contributing to the problem.

General conclusions

The pathophysiology of pulmonary hypertension cannot be fully understood in terms of a traditional single cause and effect model. The concept of a balance of factors is probably more helpful. Under different circumstances three general, often interrelated, types of response are apparent: vasodilation/vasospasm, mitogenesis/cytostasis, and thrombosis/fibrinolysis. Although the vascular response to insult often appears relatively stereotyped, causes are invariably multifactorial. Genetic, environmental, nutritional, gender related factors and comorbidities are all likely to influence the final outcome. Serotonin is clearly an important and pervasive pro-inflammatory influence in these processes. Most authorities are now in agreement that serotonergic mechanisms are important in the pathogenesis of dietary pulmonary hypertension.^{63 64 80 185} The role of serotonin in other varieties of pulmonary hypertension has been unjustly neglected.

The evaluation of effective therapies for this serious disorder demands a much better understanding of the precise mechanisms involved in different clinical situations and in different stages of the disease. In many variants the patients are young, the prognosis is very poor, and the clinical management is difficult. Vasodilator therapy in isolation is frequently ineffective. A multifaceted approach to treatment including antiserotonin agents or platelet modifying drugs may prove to be more successful.

1 Rounds S, Hill NS. Pulmonary hypertensive diseases. *Chest* 1984;85:397-405.

2 Alpert JS, Irwin RS, Dalen JE. Pulmonary hypertension. *Dis Mon* 1981;5:1-39.

- 3 Reid LM. Structure and function in pulmonary hypertension. *Chest* 1986;**89**:279–88.
- 4 Chouat A, Weitzenblum E, Higgenbottam T. The role of thrombosis in severe pulmonary hypertension. *Eur Respir J* 1996;**9**:356–63.
- 5 Cool CD, Kennedy D, Voelkel NF, et al. Pathogenesis and evolution of plexiform lesions in pulmonary hypertension associated with scleroderma and human immunodeficiency virus infection. *Hum Pathol* 1997;**28**:434–42.
- 6 Rubin LJ. Introduction. In: Rubin LJ, ed. *Pulmonary heart disease*. Boston: Martinus Nijhoff, 1984: 1–10.
- 7 Cooper R, Ghali J, Simmons BE, et al. Elevated pulmonary artery pressure. An independent predictor of mortality. *Chest* 1991;**99**:112–20.
- 8 Draughn D, Morris DM. Sustained pulmonary hypertension in surgical patients. *Am Surg* 1993;**59**:346–9.
- 9 Keller CA, Shepard JW, Chun DS, et al. Pulmonary hypertension in chronic obstructive pulmonary disease. Multivariate analysis. *Chest* 1986;**90**:185–92.
- 10 Bitterman PB, Henke CA. Fibroproliferative disorders. *Chest* 1991;**99**:81–6S.
- 11 Hart CM, Block ER. Lung serotonin metabolism. *Clin Chest Med* 1989;**10**:59–70.
- 12 Perry RR, Vinik AI. Endocrine tumors of the GI tract. *Annu Rev Med* 1996;**47**:59–62.
- 13 Lockhart A. Pulmonary arterial hypertension in portal hypertension. *Clin Gastroenterol* 1985;**14**:123–38.
- 14 Mandell MS, Groves BM. Pulmonary hypertension in chronic liver disease. *Clin Chest Med* 1996;**17**:17–33.
- 15 Katz AL, Massry SG, Tikvah P. Arteriospasm after ergotamine tartrate in infectious hepatitis. *Arch Intern Med* 1966;**118**:62–4.
- 16 Block ER, Stalcup A. Metabolic functions of the lung. Of what clinical relevance? *Chest* 1982;**81**:215–23.
- 17 Boor PJ, Hysmith RM, Sanduja R. A role for a new vascular enzyme in the metabolism of xenobiotic amines. *Circ Res* 1990;**66**:249–52.
- 18 Wiedemann HP, Mathay MA, Gillis CN. Pulmonary endothelial cell injury and altered lung metabolic function. *Clin Chest Med* 1990;**11**:723–36.
- 19 Sole MJ, Drobac M, Schwartz L, et al. The extraction of circulating catecholamines by the lungs in normal man and in patients with pulmonary hypertension. *Circulation* 1979;**60**:160–3.
- 20 Johnson DA, Georgieff MK. Pulmonary neuroendocrine cells. Their secretory products and their potential roles in lung and chronic lung disease in infancy. *Am Rev Respir Dis* 1989;**140**:1807–12.
- 21 Lauweryns JM, de Bock V, Guelinckx P, et al. Effects of unilateral hypoxia on neuroepithelial bodies in rabbit lungs. *J Appl Physiol* 1983;**55**:1665–8.
- 22 Gosney J, Heath D, Smith P, et al. Pulmonary endocrine cells in pulmonary arterial disease. *Arch Pathol Lab Med* 1989;**113**:337–41.
- 23 Madden BP, Gosney J, Coghlan JG, et al. Pretransplant clinicopathological correlation in end-stage primary pulmonary hypertension. *Eur Respir J* 1994;**7**:672–8.
- 24 Breuer J, Georgeraki A, Seiverding L, et al. Increased turnover of serotonin in children with pulmonary hypertension secondary to congenital heart disease. *Pediatr Cardiol* 1996;**17**:214–9.
- 25 Schindler MB, Bohn DJ, Bryan AC, et al. Increased respiratory resistance and bronchial smooth muscle hypertrophy in children with acute postoperative pulmonary hypertension. *Am J Respir Crit Care Med* 1995;**152**:1347–52.
- 26 Keith I, Day R, Lemaire S, et al. Asbestos-induced fibrosis in rats: increase in lung mast cells and autacid contents. *Exp Lung Res* 1987;**13**:311–27.
- 27 Nakano T, Miyamoto K, Nishimura M, et al. Role of pulmonary intravascular macrophages in anti-platelet serum-induced pulmonary hypertension in sheep. *Respir Physiol* 1994;**98**:83–9.
- 28 Jubelirer SJ. Primary pulmonary hypertension. Its association with microangiopathic hemolytic anemia and thrombocytopenia. *Arch Intern Med* 1991;**151**:1221–3.
- 29 McGoon MD, Vanhoutte PM. Aggregating platelets contract isolated canine pulmonary arteries by releasing 5-hydroxytryptamine. *J Clin Invest* 1984;**74**:828–33.
- 30 Bennett JS, Kolodziej MA. Disorders of platelet function. *Dis Mon* 1992;**28**:577–631.
- 31 Nakonechnicov S, Gabbasov Z, Chazova I, et al. Platelet aggregation in patients with primary pulmonary hypertension. *Blood Coagul Fibrinol* 1996;**7**:225–7.
- 32 Tudor RM, Groves B, Badesch DB, et al. Exuberant endothelial cell growth and elements of inflammation are present in plexiform lesions of pulmonary hypertension. *Am J Pathol* 1994;**144**:275–85.
- 33 Rabinovitch M, Andrew M, Thom H, et al. Abnormal endothelial factor VIII associated with pulmonary hypertension and congenital heart defects. *Circulation* 1987;**76**:1043–52.
- 34 Schnader J, Schloo BL, Anderson W, et al. Chronic pulmonary hypertension in sheep: temporal progression of lesions. *J Surg Res* 1996;**62**:243–50.
- 35 Wu KK. Platelet activation mechanisms and markers in arterial thrombosis. *J Intern Med* 1996;**239**:17–34.
- 36 Moore GW, Smith RR, Hutchins GM. Pulmonary artery atherosclerosis: correlation with systemic atherosclerosis and hypertensive pulmonary vascular disease. *Arch Pathol Lab Med* 1982;**106**:378–80.
- 37 Herve P, Launay JM, Scrobhaci ML, et al. Increased plasma serotonin in primary pulmonary hypertension. *Am J Med* 1995;**99**:249–54.
- 38 Constanides P, Robinson M. Effects of vasoactive amines. *Arch Pathol* 1969;**88**:106–12.
- 39 Moore LK, Burt JM. Gap function in vascular smooth muscle: influence of serotonin. *Am J Physiol* 1995;**269**:H1481–9.
- 40 Heffner JE, Sahn SA, Repine JE. The role of platelets in the adult respiratory distress syndrome. Culprits or bystanders? *Am Rev Respir Dis* 1987;**135**:482–92.
- 41 Comroe JH, van Lingen B, Stroud RC. Reflex and direct cardiopulmonary effects of 5 OH tryptamine (serotonin). Their possible role in pulmonary embolism and coronary thrombosis. *Am J Physiol* 1953;**173**:379–86.
- 42 Reneman RS, van der Starre PJ. Serotonin and acute cardiovascular disorders. *Cardiovasc Drugs Ther* 1990;**4**(Suppl 1):19–25.
- 43 Brogden RN, Sorkin EM. Ketanserin. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in hypertension and peripheral vascular disease. *Drugs* 1990;**40**:903–49.
- 44 Buckner CK, Dea D, Liberati N, et al. A pharmacologic examination of receptors mediating serotonin-induced bronchoconstriction in the anesthetized guinea pig. *J Pharmacol Exp Ther* 1991;**257**:26–34.
- 45 Pakala R, Willerson JT, Benedict CR. Mitogenic effect of serotonin on vascular endothelial cells. *Circulation* 1994;**90**:1919–26.
- 46 Hauck AJ, Edwards WD, Danielson GK, et al. Mitral and aortic valve disease associated with ergotamine therapy for migraine. Report of two cases and review of literature. *Arch Pathol Lab Med* 1990;**114**:62–4.
- 47 Lee SL, Wang WW, Joseph PM, et al. Inhibitory effect of heparin on serotonin-induced hyperplasia and hypertrophy of smooth muscle cells. *Am J Respir Cell Mol Biol* 1997;**17**:78–83.
- 48 Fanburg BL, Lee SL. A new role for an old molecule: serotonin as a mitogen. *Am J Physiol* 1997;**272**:L795–806.
- 49 Cooke JP, Dzau VJ. Nitric oxide synthase: role in the genesis of vascular disease. *Annu Rev Med* 1997;**48**:489–509.
- 50 Campbell JH, Campbell GR. Vascular smooth muscle in culture and its relevance to the study of atherogenesis. In: Page C, Black J, eds. *Airways and vascular remodelling in asthma and cardiovascular disease*. London: Academic Press Harcourt Brace, 1994: 27–37.
- 51 Rabinovitch M. Investigational approaches to pulmonary hypertension. *Toxicol Pathol* 1991;**19**:458–69.
- 52 Scott PH, Peacock AJ. Cell signalling in pulmonary vascular cells: do not shoot the messenger! *Thorax* 1996;**51**:864–6.
- 53 Kay JM, Keane PM, Suyama KL. Pulmonary hypertension induced in rats by monocrotaline and chronic hypoxia is reduced by p-chlorophenylalanine. *Respiration* 1985;**47**:48–56.
- 54 Eddahibi S, Raffestin B, Pham I, et al. Treatment with 5-HT potentiates development of pulmonary hypertension in chronically hypoxic rats. *Am J Physiol* 1997;**272**:H1173–81.
- 55 Gyermek L. Pharmacology of serotonin as related to anesthesia. *J Clin Anesth* 1996;**8**:402–25.
- 56 Frishman WH, Huberfeld S, Okin S, et al. Serotonin and serotonin antagonism in cardiovascular and non-cardiovascular disease. *J Clin Pharmacol* 1996;**35**:541–72.
- 57 Zeiher AM, Schachinger V, Hohnloser SH, et al. Coronary atherosclerotic wall thickening and vascular reactivity in humans. Elevated high-density lipoprotein levels ameliorate abnormal vasoconstriction in early atherosclerosis. *Circulation* 1994;**89**:2525–32.
- 58 Steyn DW, Odendaal HJ. Randomised controlled trial of ketanserin and aspirin in prevention of pre-eclampsia. *Lancet* 1997;**350**:1267–71.
- 59 Morcos NC, Purdy RE, Henry WL. Vasoreactivity in isolated perfused atherosclerotic human coronary arteries. *Int J Tissue React* 1988;**10**:159–67.
- 60 McFadden EP, Clarke JG, Davies GJ, et al. Effect of intracoronary serotonin on coronary vessels in patients with stable angina and patients with variant angina. *N Engl J Med* 1991;**324**:648–54.
- 61 Drouet L, Sollier BD, Ruton S, et al. Role of serotonin in arteriolar thrombosis and secondary vasospasm. *J Cardiovasc Pharmacol* 1990;**16**(Suppl 3):S49–53.
- 62 Siegel G, Ruckborn K, Schnalke F, et al. Endothelial dysfunction in human atherosclerotic coronary arteries. *Eur Heart J* 1993;**14**(Suppl 1):99–103.
- 63 Abenheim L, Moride Y, Brenot F, et al. Appetite suppressant drugs and the risk of primary pulmonary hypertension. *N Engl J Med* 1996;**335**:609–16.
- 64 Brenot F, Herve P, Petitpretz P, et al. Primary pulmonary hypertension and fenfluramine use. *Br Heart J* 1993;**70**:537–41.
- 65 Fristrom S, Airaksinen MM, Halmekoski J. Release of platelet 5-hydroxytryptamine by some anorexic and other sympathomimetics and their acetyl derivatives. *Acta Pharmacol Toxicol* 1977;**41**:218–24.
- 66 Naeije R, Maggiorini M, Delcroix M, et al. Effects of chronic dexfenfluramine treatment on pulmonary hemodynamics in dogs. *Am J Respir Crit Care Med* 1996;**154**:1347–50.
- 67 Seiler KU, Wasserman O, Wensky H. On the role of serotonin in the pathogenesis of pulmonary hypertension induced by anorectic drugs: an experimental study in the isolated perfused rat lung. II. Fenfluramine, mazindol, mefenorex, phentermine and R800. *Clin Exp Pharmacol Physiol* 1976;**3**:323–30.
- 68 Mielke H, Seiler KU, Stumpf U, et al. Relation between serotonin metabolism and pulmonary hypertension in rats following administration of various anorectic drugs. *Z Kardiol* 1973;**62**:1090–8.

- 69 Weir EK, Reeve HL, Huang JM, *et al.* Anorexic agents amiprone, fenfluramine, and dexfenfluramine inhibit potassium current in rat pulmonary smooth muscle and cause pulmonary vasoconstriction. *Circulation* 1996;**94**:2216–20.
- 70 Mills KC. Serotonin syndrome. A clinical update. *Med Toxicol* 1997;**13**:763–83.
- 71 Collazos J, Martinez E, Fernandez A, *et al.* Acute, reversible pulmonary hypertension associated with cocaine use. *Respir Med* 1996;**90**:171–4.
- 72 Booker PD, Evans C, Franks R. Comparison of the haemodynamic effects of dopamine and dobutamine in young children undergoing cardiac surgery. *Br J Anaesth* 1995;**74**:419–23.
- 73 Dukes MGG, ed. *Meyler's side effects of drugs*. Lausanne: Elsevier, 1996: 17.
- 74 de Kerviler E, Tredaniel J, Revlon G, *et al.* Fluoxetine-induced pulmonary granulomatosis. *Eur Respir J* 1996;**9**:615–7.
- 75 Filterborg JA. Persistent pulmonary hypertension after lithium intoxication in the newborn. *Eur J Pediatr* 1982;**138**:321–3.
- 76 Schaiberger PH, Kennedy TC, Miller FC, *et al.* Pulmonary hypertension associated with long-term inhalation of "crank" methamphetamine. *Chest* 1993;**104**:614–16.
- 77 Fujiwara M, Tobise K, Onodera S. Effects of methysergide on pulmonary circulation. *Hokkaido J Med Sci* 1983;**58**:541–2.
- 78 Radow SK, Nachamkin I, Morrow C, *et al.* Foreign body granulomatosis. Clinical and immunologic findings. *Am Rev Respir Dis* 1983;**127**:575–80.
- 79 Van der Starre PJ, Solinas C. Ketanserin in the treatment of protamine-induced pulmonary hypertension. *Texas Heart Inst J* 1996;**23**:301–4.
- 80 Voelkel NF. Appetite suppressants and pulmonary hypertension. *Thorax* 1997;**52**:563–7.
- 81 Tazelaar HD, Myers JL, Drage CW, *et al.* Pulmonary diseases associated with L-tryptophan-induced eosinophilic myalgia syndrome. Clinical and pathologic features. *Chest* 1990;**97**:1032–6.
- 82 Farber HW, Falls R, Glauser FL. Transient pulmonary hypertension from the intravenous injection of crushed suspended pentazocine tablets. *Chest* 1981;**80**:178–82.
- 83 Arnett EN, Battle WE, Russo JV, *et al.* Intravenous injection of talc-containing drugs intended for oral use. A cause of pulmonary granulomatosis and pulmonary hypertension. *Am J Med* 1976;**60**:711–8.
- 84 Spah F, Kottman R, Grossner KD, *et al.* Effects of Urapidil in patients with mild pulmonary hypertension. *Drugs* 1990;**40**(Suppl 4):69–70.
- 85 Tornebrandt K, Eskilsson J, Nobin A. Heart involvement in metastatic carcinoid disease. *Clin Cardiol* 1986;**9**:13–9.
- 86 Arora RR, Warner RR. Do indole marker predict carcinoid heart disease? *Chest* 1986;**90**:87–9.
- 87 Lundin L, Oberg K, Landelius J, *et al.* Plasma atrial natriuretic peptide in carcinoid heart disease. *Am J Cardiol* 1989;**63**:969–72.
- 88 Jacobsen MB, Nitter-Hauge S, Bryde PE, *et al.* Cardiac manifestations of mid-gut carcinoid disease. *Eur Heart J* 1995;**16**:263–8.
- 89 Robiolo PA, Rigolin VH, Wilson JS, *et al.* Carcinoid heart disease. Correlation of high serotonin levels with valvular abnormalities detected by cardiac catheterisation and echocardiography. *Circulation* 1995;**92**:790–5.
- 90 Connolly HM, Cray JL, McGoon MD, *et al.* Valvular heart disease associated with fenfluramine-phentermine. *N Engl J Med* 1997;**337**:581–8.
- 91 Eckhauser FE, Argenta LC, Strodel WE, *et al.* Mesenteric angiopathy, intestinal gangrene, and midgut tumors. *Surgery* 1981;**90**:720–8.
- 92 Gaudin PB, Rosai J. Florid vascular proliferation associated with neural and neuroendocrine neoplasms. A diagnostic clue and potential pitfall. *Am J Surg Pathol* 1995;**19**:642–52.
- 93 Wilson DW, Segall HJ, Pan LC, *et al.* Mechanisms and pathology of monocrotaline pulmonary toxicity. *Crit Rev Toxicol* 1992;**22**:307–25.
- 94 Todorovich-Hunter L, Dodo H, Ye C, *et al.* Increased pulmonary artery elastolytic activity in adult rats with monocrotaline-induced progressive hypertensive pulmonary vascular disease compared with infant rats with nonprogressive disease. *Am Rev Respir Dis* 1992;**146**:213–23.
- 95 Kanai Y, Hori S, Tanaka T, *et al.* Role of 5-hydroxytryptamine in the progression of monocrotaline induced pulmonary hypertension in rats. *Cardiovasc Res* 1993;**27**:1619–23.
- 96 Roth RA, Ganey PE. Platelets and the puzzles of pulmonary pyrrolizidine poisoning. *Toxicol Appl Pharmacol* 1988;**93**:463–71.
- 97 Ganey PE, Sprugel KH, White SM, *et al.* Pulmonary hypertension due to monocrotaline pyrrole is reduced by moderate thrombocytopenia. *Am J Physiol* 1988;**255**:H1165–72.
- 98 Hilliker KS, Roth RA. Alteration of monocrotaline pyrrole-induced cardiopulmonary effects in rats by hydralazine, dexamethasone or sulphinyprazole. *Br J Pharmacol* 1984;**82**:375–80.
- 99 Tanabe T, Furaya H, Kanemoto N, *et al.* Experimental study on monocrotaline induced pulmonary hypertensive rats. (1) Effect of long-term injection with immunosuppressants. *Tokai J Exp Clin Med* 1981;**6**:41–8.
- 100 Langleben D, Carvalho AC, Reid LM. The platelet inhibitor, dazmegrel, does not reduce monocrotaline-induced pulmonary hypertension. *Am Rev Respir Dis* 1986;**133**:789–91.
- 101 Hamilton WM, Nemir P. The humoral factor in pulmonary embolism. *Arch Surg* 1972;**105**:593–8.
- 102 Smith G, Smith AN. The role of serotonin in experimental pulmonary embolism. *Surg Gynecol Obstet* 1955;**101**:691–9.
- 103 Gurewich V, Cohen ML, Thomas DP. Humoral factors in massive pulmonary embolism: an experimental study. *Am Heart J* 1968;**76**:784–91.
- 104 Gurewich V, Thomas D, Stein M, *et al.* Bronchoconstriction in the presence of pulmonary embolism. *Circulation* 1963;**XXVII**:329–45.
- 105 Kawai A, Umeda A, Mori M, *et al.* Role of serotonin in impaired gas exchange during pulmonary embolism. *Nippon Kyobu Shikkan Gakkai Zasshi* 1995;**33**:947–55.
- 106 King AD, Bell SD, Strutt AWJ, *et al.* Platelet imaging of thromboembolism. Natural history of postoperative deep venous thrombosis and pulmonary embolism illustrated using the ¹¹¹In-labelled platelet-specific monoclonal antibody, P256. *Chest* 1992;**101**:1597–601.
- 107 Thomas DP, Gurewich V, Ashford P. Platelet adherence to thromboemboli in relation to the pathogenesis and treatment of pulmonary embolism. *N Engl J Med* 1966;**274**:953–6.
- 108 Monreal M, Lafoz E, Casals A, *et al.* Platelet count and venous thromboembolism. A useful test for suspected pulmonary embolism. *Chest* 1991;**100**:1493–6.
- 109 Williams GD, Westbrook KC, Campbell GS. Reflex pulmonary hypertension and systemic hypotension after microsphere pulmonary embolism: a myth. *Am J Surg* 1969;**118**:925–30.
- 110 Onodera S. Pulmonary vasoconstrictor responses. *Nippon Kyobu Shikkan Gakkai Zasshi* 1992;**30**(Suppl):15–25.
- 111 Mlczoch J, Tucker A, Weir EK, *et al.* Platelet-mediated hypertension and hypoxia during pulmonary microembolism: reduction by platelet inhibition. *Chest* 1978;**74**:648–53.
- 112 Huval WV, Mathieson MA, Stemp LI, *et al.* Therapeutic benefits of 5-hydroxytryptamine inhibition following pulmonary embolism. *Ann Surg* 1983;**197**:220–5.
- 113 Huet Y, Brun-Buisson C, Lemaire F, *et al.* Cardiopulmonary effects of ketanserin infusion in human pulmonary embolism. *Am Rev Respir Dis* 1987;**135**:114–7.
- 114 Breuer J, Meschig R, Breuer HW, *et al.* Effects of serotonin on the cardiopulmonary circulatory system with and without 5-HT₂ receptor blockade by ketanserin. *J Cardiovasc Pharmacol* 1985;**7**(Suppl 7):S64–6.
- 115 Siegal T, Pfeiffer MR. Radiation-induced changes in the profile of spinal cord serotonin, prostaglandin synthesis, and vascular permeability. *Int J Radiat Oncol Biol Phys* 1995;**31**:57–64.
- 116 Bremer K. 5 Hydroxytryptamine (serotonin) subtype 3 antagonists, a major step in prophylaxis and control of cytostatic and radiation-induced emesis. *J Cancer Res Clin Oncol* 1991;**117**:85–7.
- 117 Peterson LM, Evans ML, Graham MM, *et al.* Vascular response to radiation injury in the rat lung. *Radiat Res* 1992;**12**:139–48.
- 118 Gillette SM, Powers BE, Orton EC, *et al.* Early radiation response of the canine heart and lung. *Radiat Res* 1991;**125**:34–40.
- 119 Tillman BF, Lloyd JE, Malcolm AW, *et al.* Unilateral radiation pneumonitis in sheep: physiological changes and bronchoalveolar lavage. *J Appl Physiol* 1989;**66**:1273–9.
- 120 Baguley BC, Zhuang L, Kestell P. Increased plasma serotonin following treatment with flavone-8-acetic acid, 5,6-dimethylxanthone-4-acetic acid, vinblastine, and colchicine: relation to vascular effects. *Oncol Res* 1997;**9**:55–60.
- 121 Tomashefski JF, Davies P, Boggis C, *et al.* The pulmonary vascular lesions of the adult respiratory distress syndrome. *Am J Pathol* 1983;**112**:112–26.
- 122 Fowler AA, Hamman RF, Zerbe GO, *et al.* Adult respiratory distress syndrome. Prognosis after onset. *Am Rev Respir Dis* 1985;**132**:472–8.
- 123 Bone RC, Francis PB, Pierce AK. Intravascular coagulation associated with the adult respiratory distress syndrome. *Am J Med* 1976;**61**:585–9.
- 124 Carvalho AC, Quinn DA, De Marinis SM, *et al.* Platelet function in acute respiratory failure. *Am J Haematol* 1987;**25**:377–88.
- 125 Fein A, Lippmann H, Hotzman H, *et al.* The risks, incidence and prognosis of adult distress syndrome following septicemia. *Chest* 1983;**83**:40–2.
- 126 Sibbald W, Peters S, Lindsay RM. Serotonin and pulmonary hypertension in human septic ARDS. *Crit Care Med* 1980;**8**:490–4.
- 127 Kasajima K, Ozdemir A, Webb WR, *et al.* Role of serotonin and serotonin antagonist on pulmonary hemodynamics and microcirculation in hemorrhagic shock. *J Thorac Cardiovasc Surg* 1974;**67**:908–14.
- 128 Vincent JL, Degaute JP, Domb M, *et al.* Ketanserin, a serotonin antagonist. Administration in patients with acute respiratory failure. *Chest* 1984;**85**:510–3.
- 129 Asherson RA, Oakley C. Pulmonary hypertension and systemic lupus erythematosus. *J Rheumatol* 1986;**13**:1–5.
- 130 Murata I, Takenaka K, Yoshinoya S, *et al.* Clinical evaluation of pulmonary hypertension in systemic sclerosis and related disorders. A doppler echocardiographic study of 135 Japanese patients. *Chest* 1997;**111**:36–43.
- 131 Battle RW, Davitt MA, Cooper SM, *et al.* Prevalence of pulmonary hypertension in limited and diffuse scleroderma. *Chest* 1996;**110**:1515–9.

- 132 Wiedemann HP, Matthay RA. Pulmonary manifestations of collagen vascular diseases. *Clin Chest Med* 1989;10:677-723.
- 133 Marasini B, Biondini ML, Bianchi E, et al. Ketanserin treatment and serotonin in patients with primary and secondary Raynaud's phenomenon. *Eur J Clin Pharmacol* 1988;35:419-21.
- 134 Klimiuk PS, Grennan A, Weinkove C, et al. Platelet serotonin in systemic sclerosis. *Ann Rheum Dis* 1989;48:586-9.
- 135 Stachow A, Jablonska S, Skindzielewska A. Biogenic amines derived from tryptophan in systemic and cutaneous scleroderma. *Acta Dermat Venereol* 1979;59:1-5.
- 136 Seibold JR, Molony RR, Turkevich D, et al. Acute hemodynamic effects of ketanserin in pulmonary hypertension secondary to systemic sclerosis. *J Rheumatol* 1987;14:519-24.
- 137 Hadengue A, Benhayoun MK, Lebrec D, et al. Pulmonary hypertension complication portal hypertension, prevalence and relation to splanchnic hemodynamics. *Gastroenterology* 1991;100:520-8.
- 138 Edwards BS, Weir EK, Edwards WD, et al. Coexistent pulmonary and portal hypertension: morphological and clinical features. *J Am Coll Cardiol* 1987;10:1233-8.
- 139 Voelkel NF. State of the art. Mechanisms of hypoxic pulmonary vasoconstriction. *Am Rev Respir Dis* 1986;133:1186-95.
- 140 MacLean MR, Clayton RA, Hillis SW, et al. 5-HT₁-receptor mediated vasoconstriction in bovine isolated pulmonary arteries: influences of vascular endothelium and tone. *Pulm Pharmacol* 1994;7:65-72.
- 141 Demiryurek AT, Wadsworth RM, Kane KA, et al. The role of endothelium in hypoxic constriction of human pulmonary artery rings. *Am Rev Respir Dis* 1993;147:283-90.
- 142 Rahda TG, Venkatasubramanian TA, Viswanathan R. Effect of acute hypoxia on blood serotonin in human beings and rats. *Respiration* 1976;33:64-9.
- 143 Bobrov VA, Fushstei IM, Polivoda SN. Pulmonary hemodynamics and serotonin level in patients with chronic pneumonia with arterial hypertension. *Vrach Delo* 1985;12:33-5.
- 144 Pribilova NN. Serotonin metabolism and pulmonary hypertension in chronic lung diseases. *Sov Med* 1976;12:107-11.
- 145 Rostagno C, Prisco D, Boddi M, et al. Evidence for local platelet activation in pulmonary vessels in patients with pulmonary hypertension secondary to chronic obstructive pulmonary disease. *Eur Respir J* 1991;4:147-51.
- 146 Zhang X, Ling P. Platelet activation in patients with chronic pulmonary heart disease. Effect of dipyridamole treatment. *Chin Med J* 1995;108:95-7.
- 147 Steele P, Ellis JH, Weilly HS, et al. Platelet survival time in patients with hypoxemia and pulmonary hypertension. *Circulation* 1977;55:660-1.
- 148 Segall M, Goetzman B. Hypoxic pulmonary hypertension: changes in platelet size and number. *Am J Perinatol* 1991;8:300-3.
- 149 Nenci GG, Berretini M, Todisco T, et al. Exhausted platelets in chronic obstructive pulmonary disease. *Respiration* 1983;44:71-6.
- 150 Nenci GG, Berretini M, Todisco T, et al. Effects of dipyridamole on the hypoxemic pulmonary hypertension of patients with chronic obstructive pulmonary disease. *Respiration* 1988;53:13-9.
- 151 Ran PX, Duan SF. The effects of persantine on pulmonary artery pressure of rats exposed to hypoxia. *Chinese J Tuberc Respir Dis* 1993;16:216-7, 252-3.
- 152 Keith IM, Will JA, Huxtable RJ, et al. Anti-platelet agents reduce morphological changes of chronic hypoxic pulmonary hypertension. *Histol Histopathol* 1987;2:203-6.
- 153 Herve P, Drouet L, Dosquet C, et al. Primary pulmonary hypertension in a patient with familial platelet storage pool disease: role of serotonin. *Am J Med* 1990;89:117-20.
- 154 Sato K, Webb S, Tucker A, et al. Factors influencing the idiopathic development of pulmonary hypertension in the fawn hooded rat. *Am Rev Respir Dis* 1992;145:793-7.
- 155 Janakidevi K, Tiruppathi C, del Vecchio PJ, et al. Growth characteristics of pulmonary artery smooth muscle cells from fawn-hooded rats. *Am J Physiol* 1995;268:L465-70.
- 156 Ashmore RC, Rodman DM, Sato K, et al. Paradoxical constriction to platelets by arteries from rats with pulmonary hypertension. *Am J Physiol* 1991;260:929-34.
- 157 Hilliker K, Bell TG, Roth RA. Monocrotaline pyrrole-induced pulmonary hypertension in fawn-hooded rats with platelet storage pool deficiency: 5-hydroxytryptamine uptake by isolated perfused lungs. *Thromb Haemost* 1983;50:844-7.
- 158 Stelzner T, Hofmann TA, Brown D, et al. Genetic determinants of pulmonary hypertension in fawn-hooded rats. *Chest* 1997;111:96S.
- 159 Schafer AI. Bleeding and thrombosis in the myeloproliferative disorders. *Blood* 1984;64:1-12.
- 160 Reisner SA, Rinkevich D, Markevich W, et al. Cardiac involvement in patients with myeloproliferative disorders. *Am J Med* 1992;93:498-504.
- 161 Moore A, Nachman RL. Platelet Fc receptor: increased expression in myeloproliferative disease. *J Clin Invest* 1981;67:1064.
- 162 Gralnick HR, Vail M, McKeown LP, et al. Activated platelets in paroxysmal nocturnal haemoglobinuria. *Br J Haematol* 1995;91:697-702.
- 163 Heller PG, Grinberg AR, Lencioni M, et al. Pulmonary hypertension in paroxysmal nocturnal hemoglobinuria. *Chest* 1992;102:642-3.
- 164 Spencer A. Paroxysmal nocturnal haemoglobinuria in pregnancy: a case report. *Br J Obstet Gynaecol* 1980;87:246-8.
- 165 Auger WR, Permpikul P, Moser KM. Lupus anticoagulant, heparin use, and thrombocytopenia in patients with chronic thromboembolic pulmonary hypertension. A preliminary report. *Am J Med* 1995;99:392-6.
- 166 Hillderdal G. The lung physician and the antiphospholipid syndrome. *Eur Respir J* 1997;10:511-2.
- 167 Arnout J. The pathogenesis of the antiphospholipid syndrome: a hypothesis based on parallelisms with heparin-induced thrombocytopenia. *Thromb Haemost* 1996;75:155-41.
- 168 Schafer AI, Kroll MH. Nonatheromatous arterial thrombosis. *Annu Rev Med* 1993;144:155-70.
- 169 Segall ML, Goetzman BW, Schick JB. Thrombocytopenia and pulmonary hypertension in perinatal aspiration syndrome. *J Pediatr* 1980;96:727-30.
- 170 Horgan MJ, Carrasco NJM, Risemberg H. The relationship of thrombocytopenia to the onset of persistent pulmonary hypertension of the newborn in the meconium aspiration syndrome. *NY State J Med* 1985;85:245-7.
- 171 McGoon MD, Vliestra RE. Vasodilator therapy for primary pulmonary hypertension. *Mayo Clin Proc* 1984;59:672-7.
- 172 McGoon MD, Vliestra RE. Acute hemodynamic response to the 5₂-serotonergic receptor antagonist, ketanserin, in patients with primary pulmonary hypertension. *Int J Cardiol* 1987;14:303-9.
- 173 Van der Starre PJ, Reneman RS. The role of serotonin blockers in cardiac anesthesia. *J Cardiothorac Vasc Anesth* 1994;8:455-62.
- 174 Van der Starre PJ, Feld RJ, Reneman RS. Ketanserin in the treatment of pulmonary hypertension after valvular surgery: a comparison with nitroprusside. *Crit Care Med* 1989;17:613-8.
- 175 Radermacher P, Huet Y, Pluskwa F, et al. Comparison of ketanserin and sodium nitroprusside in patients with severe ARDS. *Anesthesiology* 1988;68:152-7.
- 176 Hamet A, Kral B, Cernohorsky D. Comparative effects of oxygen, nifedipine and ketanserin in hypoxic pulmonary hypertension. *Cor et Vasa* 1985;27:406-11.
- 177 Huval WV, Lecluc S, Feingold H, et al. Effects of nitroprusside and ketanserin upon pulmonary edema after acid injury. *Surg Gynecol Obstet* 1988;166:527-34.
- 178 Martin TR, Cohen ML, Drazen JM. Serotonin-induced pulmonary responses are mediated by the 5HT₁ receptor in the mouse. *J Pharmacol Exp Ther* 1994;268:104-9.
- 179 Svartholm E, Bergqvist D, Lindblad B, et al. Pulmonary vascular response to live *Escherichia coli*: influences of different antiplatelet substances. *Circ Shock* 1987;22:173-83.
- 180 Deming RH, Wong C, Fox R, et al. Relationship of increased lung serotonin levels to endotoxin-induced pulmonary hypertension in sheep. Effect of a serotonin antagonist. *Am Rev Respir Dis* 1985;132:1257-61.
- 181 Olson NC. Role of 5-hydroxytryptamine in endotoxin-induced respiratory failure of pigs. *Am Rev Respir Dis* 1987;135:93-9.
- 182 Desmecht D, Linden A, Amory H, et al. Hemodynamic responses to *Pasteurella haemolytica* inoculation in calves given type 2 serotonergic antagonist. *Can J Physiol Pharmacol* 1996;74:572-9.
- 183 Takeda J, Masuda J, Fukushima K. Droperidol prevents serotonin-induced bronchospasm, pulmonary hypertension, and intrapulmonary shunt. *Anesth Analg* 1992;74:316.
- 184 Breuer J, Meschig R, Breuer HW, et al. Effects of serotonin on the cardiopulmonary circulation system with and without 5-HT₁ receptor blockade by ketanserin. *J Cardiovasc Pharmacol* 1985;7(Suppl 7):S64-6.
- 185 McCann UD, Seiden LS, Rubin LJ, et al. Brain serotonin neurotoxicity and primary pulmonary hypertension from fenfluramine and dexfenfluramine. *JAMA* 1997;277:563-7.
- 186 Colman RW, Hirsh J, Marder VJ, et al, eds. *Haemostasis and thrombosis: basic principles and clinical practice*. Philadelphia: JB Lippincott, 1994.