

# Plexogenic arteriopathy

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## History of a name

In 1973 a committee of the World Health Organisation convened in Geneva to discuss "primary pulmonary hypertension". On that occasion it was considered essential to provide a definition of this condition, which clinically formed an entity but morphologically showed a greatly varied picture. Pathologists were familiar with a morphological entity, commonly found in congenital cardiac shunts, occasionally in diseases of the liver, and rarely without any identifiable cause. That morphological entity had been studied particularly in patients with congenital heart disease<sup>1</sup> because it occurred far more frequently here than in the other groups. Another reason was that lung biopsy samples taken during surgical correction of the defect provided the chance to observe this form of hypertensive pulmonary vascular disease in various stages,<sup>2</sup> and not only at the end stage at necropsy. It became clear that in this entity there is a sequence of lesions, beginning with an increased muscularity of the muscular pulmonary arteries, followed by an intimal reaction, culminating in a characteristic type of intimal fibrosis. In the final stages other arterial alterations appear of which the so-called plexiform lesion is the most striking and characteristic. It was the condition with this morphological pattern of lung vessels that had always fitted the definition of primary pulmonary hypertension as used by the pathologists, sometimes preceded by the word "classical".

During the committee meeting the point was made that pathologists cannot diagnose an elevated pulmonary arterial pressure and, therefore, rather than using the term "primary pulmonary hypertension" should create their own name for the morphological entity. The task of doing this was assigned to the two pathologists on the committee, Heath and Wagenvoort who, during a luncheon on 17 October 1973, arrived at the following conclusions.

1. The various changes in this form of hypertensive pulmonary vascular disease occur exclusively in the pulmonary arteries.
2. The most characteristic histological feature of the condition is the plexiform lesion, and a new designation should refer to this alteration.
3. Plexiform lesions occur only in the final stages.

To identify the disease as a whole including the earlier stages, it was suggested that the word "plexogenic" (indicating a potential development not necessarily the presence of the lesions) rather than "plexiform" should be incorporated in the term. The proposal of the

pathologists to call the morphological entity "pulmonary arterial plexogenic disease" or "plexogenic arteriopathy" was proposed, accepted by the committee, and subsequently published as a recommendation in its report.<sup>3</sup>

Although the term "plexogenic arteriopathy" has been widely used since then, there has been some confusion. The difference between plexiform and plexogenic has not always been appreciated, so that terms such as "plexiform arteriopathy" and "plexogenic lesions" occasionally found their way into the literature, usually erroneously but sometimes on purpose. "Plexiform arteriopathy" has been used to indicate the stage of plexogenic arteriopathy in which plexiform lesions had developed. "Plexogenic lesions" have sometimes been used to denote all arterial changes of the pattern of plexogenic arteriopathy. Use of the words in these senses cannot be recommended as it tends to confuse the meaning of the original terms.

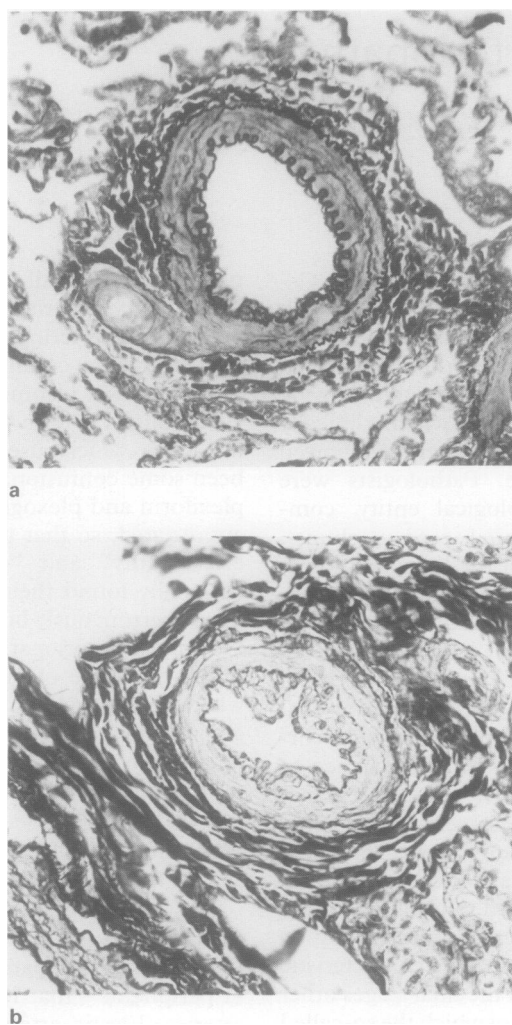
## Morphology

Plexogenic arteriopathy is essentially a disease of peripheral – that is, muscular – pulmonary arteries. Elastic arteries, including main pulmonary arteries and pulmonary trunk, may develop secondary changes such as thickening of the media and atheromatous plaques.<sup>4</sup> These alterations are associated with pulmonary hypertension in general, however, and may also be observed in other forms of hypertensive pulmonary vascular disease. Pulmonary veins are not usually involved. Only when there is additional pulmonary venous hypertension, as in some more complex cardiac defects or in late stage cardiac insufficiency, do the venous walls become thickened and may resemble those of arteries. Such venous changes complicate the pattern of plexogenic arteriopathy rather than being part of it.

### INCREASED MUSCULARITY

The early stages of plexogenic arteriopathy can easily be studied when lung biopsy samples are regularly taken during closure of congenital cardiac shunts. It then appears that the first alteration of this pattern is an increased muscularity of muscular pulmonary arteries and arterioles, which may be revealed in various ways.

Thickening of the arterial media or *medial hypertrophy* is the most common form (fig 1a). This thickening, which appears to be roughly proportional to pressure and resistance in the pulmonary circulation,<sup>5</sup> is brought about by an increase in both the size and number of its smooth muscle cells so that there is hyperplasia



**Figure 1** (a) Muscular pulmonary artery with thickening of the media giving rise to a muscularised arteriole and (b) intimal longitudinal smooth muscle bundles in a small muscular artery in patients with a ventricular septal defect. Stain: elastic van Gieson, magnification  $\times 140$  (a) and  $\times 230$  (b) reduced to 86% in origination.

as well as hypertrophy.<sup>6</sup> The medial thickness, which in normal muscular pulmonary arteries is in the range of 4–5% of the external diameter of the vessel may increase to 20% or more. In infants and young children the overall increase in muscularity may be exceedingly great. In these instances there may be an increased risk of vasoconstrictive crises of the pulmonary arteries during surgical procedures or immediately thereafter.<sup>7</sup>

Pulmonary arterial branches of a calibre of 100–70  $\mu\text{m}$  or less normally lose their muscular coat. With decreasing calibre the media becomes interrupted because the circular layer of smooth muscle cells tends to pursue a spiral course in these small, predominantly intracinar, arterioles. As a result the cells become more and more separated from each other and finally all smooth muscle cells disappear. In plexogenic arteriopathy muscularisation of arterioles, which as a rule is associated with medial hypertrophy, contributes to the increased arterial muscularity. The new smooth muscle cells are almost certainly formed ad hoc by transformation from pericytes and so-called “intermediate cells”.<sup>8</sup> Very small arterioles with a diameter of 20–40  $\mu\text{m}$  may now have a com-

plete circularly arranged muscular coat (fig 1a).

Apart from clinical and physiological evidence for vasoconstriction there are also morphological indications for prominent arterial contraction in plexogenic arteriopathy, particularly at an ultrastructural level. Crenation of an internal elastic lamina and cytoplasmic excrescences on the surface of smooth muscle cells result either from collapse of an artery or from contraction. However, these features are usually far more conspicuous as a result of constriction than of collapse. More importantly, if collapse is abolished by instillation of fixative or by in vacuum fixation, the effects of collapse on the vascular wall disappear while those of vasoconstriction remain. Vasoconstriction may, of course, contribute considerably to the thickness of the media. In some cases it is necessary to calculate the surface area of arterial smooth muscle per surface area of lung tissue to establish the presence of medial hypertrophy with certainty.

When there is vasodilatation the effect on the arterial wall is the opposite to that of vasoconstriction in that the medial thickness decreases while the arterial diameter and the width of the lumen increase. If there is generalised vasodilatation in a patient with prominent pulmonary arterial medial hypertrophy the average media may seem completely normal when compared with the external diameter. When the total medial surface area in relation to lung surface area is assessed, however, the presence of medial hypertrophy will become clear. This situation may occur when there is a large flow through the pulmonary circulation, as sometimes is seen in an atrial septal defect.

Increased muscularity is occasionally expressed in the form of longitudinal smooth muscle bundles within the intima of muscularised arterioles (fig 1b).<sup>9</sup> These bundles probably enhance the effect of vasoconstriction as, by their contraction, they will tend to narrow or obstruct the lumen. Sphincter-like structures may also be found in association with medial hypertrophy in plexogenic arteriopathy. These structures occur exclusively at the origin of a branch from a parent artery and usually protrude into the lumen of the latter.

#### INTIMAL LESIONS

The intimal lesions in plexogenic arteriopathy are always preceded by medial hypertrophy. During intense vasoconstriction the endothelial cells may become swollen while protruding into the lumen. This is particularly striking in infants. However, intimal proliferation is uncommon in the first year, even though medial hypertrophy of arteries and muscularisation of arterioles may be very pronounced. The form of intimal reaction characteristic of plexogenic arteriopathy occurs in two phases: cellular proliferation and intimal fibrosis.

In sustained pulmonary hypertension due to plexogenic arteriopathy *cellular intimal proliferation* is a fairly common lesion, particularly of small pulmonary arteries (fig 2a). Here the lumen is narrowed by the proliferating cells,

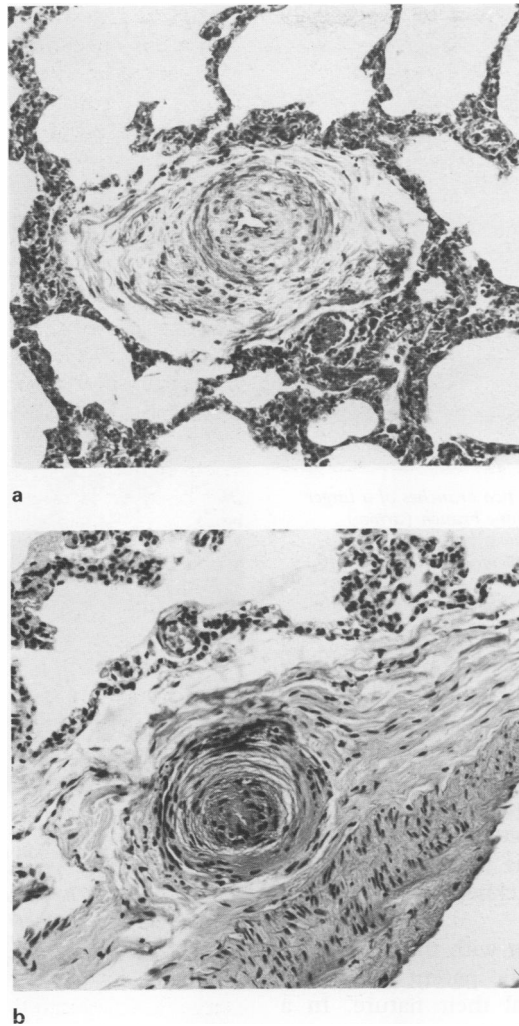


Figure 2 Small muscular pulmonary arteries in ventricular septal defect. (a) Narrowing by cellular intimal proliferation and (b) by concentric laminar (onion skin) intimal fibrosis. Stain: haematoxylin and eosin (a) and elastic van Gieson (b), magnification  $\times 180$  reduced to 86% in origination.

which have a clear cytoplasm and round or oval nuclei. At an ultrastructural level these cells in many respects resemble myofibroblasts<sup>10,11</sup> or smooth muscle cells that have lost their elongated shape. It is very likely that these cells are derived from medial smooth muscle cells, penetrating the internal elastic lamina through its fenestrations.<sup>12</sup> The cells form a layer of increasing thickness, particularly in an area close to the origin of a branch from a larger artery. They may obstruct the vessel almost completely, although a slit-like lumen is usually recognisable. Initially collagen fibres are not present, but they gradually appear in the transition to the next stage, the intimal fibrosis.

Collagen fibres usually predominate in the development of intimal fibrosis but in some cases elastic fibres are particularly numerous. Whatever the nature of the fibres, the characteristic feature of this type of intimal fibrosis is their arrangement in a peculiar fashion. Around the central lumen, or its remnant in severe cases, there are concentric layers which produce an onion skin appearance (fig 2b). This *concentric laminar intimal fibrosis* is not only characteristic but also pathognomic for plexogenic

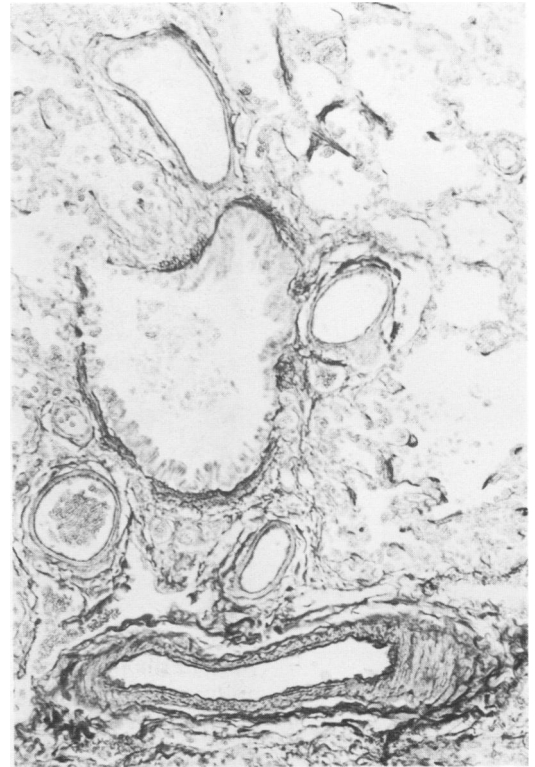


Figure 3 Dilatation lesions ("vein-like branches") in several branches of a parent artery with medial hypertrophy. Stain: elastic van Gieson, original magnification  $\times 140$  reduced to 86% in origination.

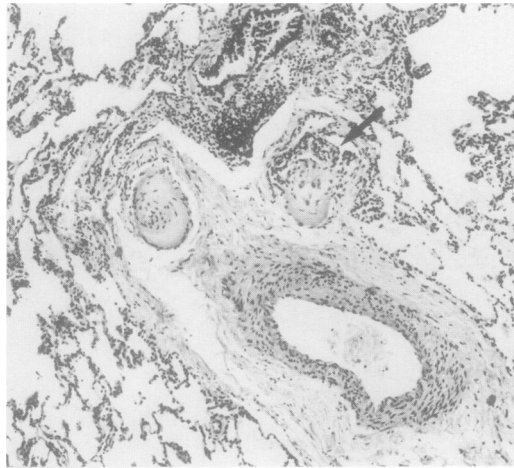
arteriopathy. It has a tendency to occlude arteries completely, and is then often associated with irreversible hypertension.

There are some other intimal lesions that are regularly seen in plexogenic arteriopathy. Thrombotic lesions resulting from organisation and recanalisation of thrombi are common in adult patients with plexogenic arteriopathy due to congenital cardiac shunts or in its primary form.<sup>13-15</sup> They appear as eccentric patches of intimal fibrosis without an onion skin arrangement. Often there are small recanalisation channels, or upon widening of these channels, the remnants of the organised thrombus stand out as intravascular fibrous septa. These thrombotic lesions are found increasingly with age in various forms of hypertensive pulmonary vascular disease. They clearly complicate these patterns rather than being part of them.<sup>16</sup>

Patches or layers of intimal longitudinal smooth muscle bundles have already been mentioned as part of an increased arterial muscularity. Intimal thickening may also be caused by foreign body granulomas as a result of cotton wool or gauze fibres introduced into the bloodstream during cardiac catheterization or intravenous injections.

#### DILATATION LESIONS

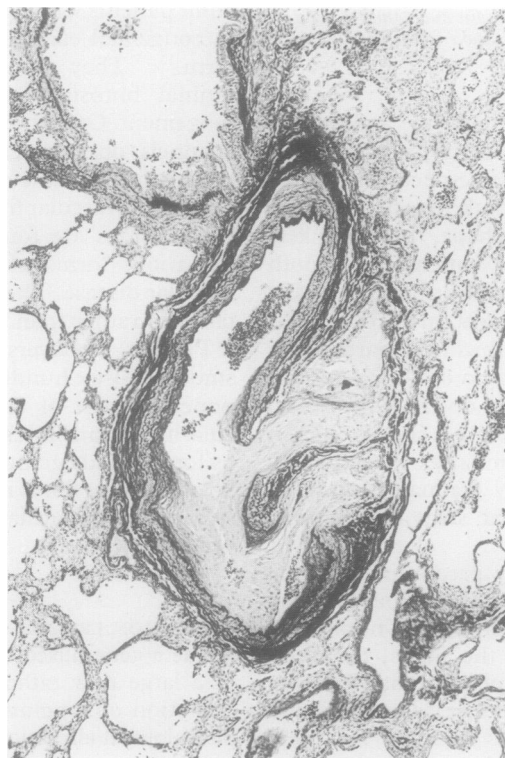
While a generalised dilatation is an adaptation to a large flow rather than a lesion, localised dilatation of a pulmonary artery constitutes a pathological alteration. This is also reflected in its ultrastructure; the smooth muscle cells of the media in the dilated segments often show pronounced degenerative changes.<sup>17</sup> Dilatation lesions are always associated with a high pres-



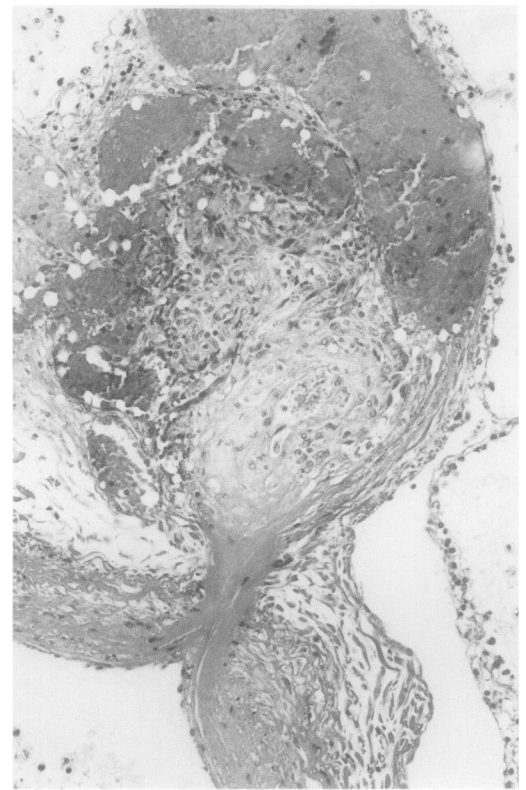
**Figure 4** Fibrinoid necrosis in two branches of a larger muscular pulmonary artery. In one branch (arrow) development of a plexiform lesion is beginning. Stain: haematoxylin and eosin, original magnification  $\times 140$  reduced to 86% in origination.

sure in the pulmonary circulation. They occur in two forms: as vein-like branches and as clusters.<sup>1</sup> Vein-like branches are thin walled wide arterial branches arising from a thick walled parent artery. Often these branches have virtually lost their media and then their recognition is easy. Sometimes, however, the thinning of the media is mild so that these branches have a wall thickness within normal limits (fig 3).

Even then the contrast with the prominent medial hypertrophy of the parent artery and other arteries will reveal their nature. In a more severe stage of pulmonary hypertension dilatation lesions may take the form of clusters



**Figure 5** Three plexiform lesions lying in branches close to their origin from a large muscular pulmonary artery. Stain: elastic van Gieson, original magnification  $\times 140$  reduced to 86% in origination.



**Figure 6** Plexiform lesion in branch arising from a parent artery (bottom left). The initial part of the branch shows fibrinoid necrosis. The plexus lies in a focal dilatation of the branch, its capillary-like channels open up in wider spaces. Stain: haematoxylin and eosin, original magnification  $\times 230$ , reduced to 84% in origination.

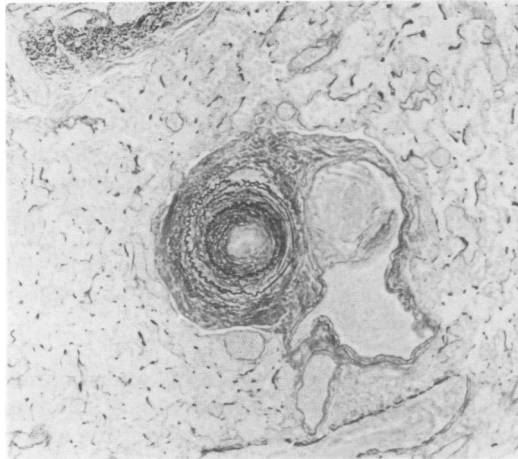
of severely dilated, very thin walled branches lying close to a parent artery. When these clusters become very large the term angiomatoid lesion applies.

#### FIBRINOID NECROSIS AND ARTERITIS

In sustained pulmonary hypertension fibrinoid necrosis may occur in muscular pulmonary arteries. Characteristically this is observed in a branch close to its origin from a larger artery and over a short distance. In such a segment most or all of the smooth muscle cells have become necrotic and the remnants of the muscular coat are replaced with fibrin and have become eosinophilic and structureless. Usually a clot consisting of fibrin and platelets lies in the lumen (fig 4).<sup>18</sup> An inflammatory reaction may be completely absent; if it occurs it is generally mild and consists of lymphocytes.

Sometimes a pronounced pulmonary arteritis is found in combination with fibrinoid necrosis in secondary or primary plexogenic arteriopathy. An infiltrate consisting predominantly of polymorphonuclear leucocytes extends throughout the arterial wall and into the adjacent lung tissue.

In such instances, however, muscular arteries of somewhat larger calibre are mostly affected, there is no topographical relation with the origin of the vessel, and the fibrinoid necrosis tends to leave more of the arterial wall intact



*Figure 7 Muscular pulmonary artery with pronounced concentric laminar intimal fibrosis. An adjacent branch contains a plexiform lesion. The branch is dilated and its wall has lost its normal elastic configuration. Stain: elastic van Gieson, original magnification  $\times 60$  reduced to 86% in origination.*

so that the media often remains clearly recognisable while even the elastic laminae may be uninterrupted. It is therefore questionable whether the two processes – fibrinoid necrosis without or with a mild reaction, and florid pulmonary arteritis with varying degrees of fibrinoid necrosis – have the same pathogenesis and clinical significance.

#### PLEXIFORM LESIONS

The plexiform lesion is the hallmark of plexogenic arteriopathy. It has a rather complicated structure but generally it is easy to identify, although there are exceptions. A plexiform lesion is located in a pulmonary arterial branch shortly after its origin from a larger artery (fig 5). They may occur distal to a dichotomous ramification point but are particularly observed in supernumerary arteries,<sup>19</sup> branches that arise perpendicularly from a large muscular pulmonary artery, or even from an elastic pulmonary artery. In its classical form it consists of a plexus of small vessels within a focal dilatation of the arterial branch. The wall at the site of this dilatation shows signs of old or fresh fibrinoid necrosis. The media has often disappeared in part or as a whole and the elastic laminae are rarely intact; usually they show interruptions or fragmentation.<sup>20</sup> Traces of fibrin are often recognisable in this damaged arterial wall or centrally in the plexus (fig 6). The plexus is formed by capillary-like channels lying close together, separated by proliferating cells which, at the electron microscopical level, have a structure not of endothelial cells but of myofibroblasts or smooth muscle cells.<sup>21</sup> These have hyperchromatic nuclei, which makes the plexiform lesion easily identifiable in a haematoxylin stain. Distal to the plexiform lesion the arterial branch, together with its ramifications, is dilated and very thin walled (fig 7). Most plexiform lesions range in size from 200  $\mu\text{m}$  to 400  $\mu\text{m}$ <sup>22</sup> but, particularly in their early development, they may be much smaller.

#### Aetiology

Plexogenic arteriopathy has a varied aetiology. It is, as mentioned previously, most commonly associated with congenital cardiovascular shunts, particularly post-tricuspid, much less tricuspid. In most cases of congenital cardiac disease, however, especially in isolated ventricular septal defect or patent ductus arteriosus, and certainly in atrial septal defect, evolution to severe pulmonary hypertension and to the more advanced lesions of plexogenic arteriopathy does not occur or is so much delayed that the stage of increased arterial muscularity is not passed. It is difficult, however, to predict whether the course will be rapidly progressive or not.

Although obviously the size of the defect is important for the evolution of pulmonary arterial disease, it is certainly not the only factor. Some patients with a small ventricular septal defect show a rapidly progressive pulmonary vascular disease, while in others with a large defect the most advanced changes are reached only after many years or not at all. Advanced lesions are unusual in children under two years of age. However, plexiform lesions are occasionally observed in infants aged only a few months with no more than a narrow ductus arteriosus or an unremarkable atrial septal defect to account for it. This suggests that individual factors, probably related to the reactivity of the pulmonary vascular bed, are involved. Other factors that may aggravate the course of the hypertensive pulmonary vascular disease include complicated congenital cardiac anomalies such as transposition of the great arteries<sup>23</sup> and Down's syndrome.<sup>24,25</sup>

Acquired cardiac shunts, although rare, may also cause plexogenic arteriopathy. This happens occasionally when too large a surgical shunt is created between systemic and pulmonary circulations in tetralogy of Fallot, while it has also been shown in experimental animals.<sup>26</sup>

Diseases of the liver with portal hypertension such as hepatic cirrhosis are occasionally associated with pulmonary plexogenic arteriopathy.<sup>27</sup> It is likely that plexogenic arteriopathy in rare cases of Niemann-Pick's disease and Gaucher's disease is also related to involvement of the liver in these conditions. The same may apply to schistosomiasis which may cause pulmonary hypertension and plexogenic arteriopathy when there is visceral involvement with pipe stem cirrhosis of the liver.

Oral ingestion of anorectic drugs is another cause of plexogenic arteriopathy. This was first revealed during an epidemic of pulmonary hypertension in central Europe which appeared to be associated with the drug aminorex fumarate. More recently other anorectic drugs, particularly fenfluramine, have been implicated. Furthermore, plexogenic arteriopathy has been observed in the so-called toxic oil syndrome and in association with autoimmune diseases, Raynaud's phenomenon, and cases positive for the human immunodeficiency virus.<sup>28</sup>

Uncommonly severe pulmonary hypertension is observed in the absence of any demonstrable cause but with the histological pattern

of lesions seen in plexogenic arteriopathy. In adults this primary plexogenic arteriopathy occurs more frequently in women than in men; in children the sex ratio is equal. This disease may affect all ages, but occurs most commonly in adolescents and adults up to 40 years of age.

#### PATHOGENESIS

Although it appears that plexogenic arteriopathy can be caused by a variety of seemingly unrelated aetiological stimuli, the characteristic pattern of its lesions suggests that there is a common pathogenesis in these different situations. This pathogenesis is, however, likely to be complex. Almost certainly vasoconstriction of muscular pulmonary arteries plays an important part. An increased muscularity of these vessels is always the first recognisable change. Spastic crises of the pulmonary circulation, particularly in young children, are a well known problem during or following corrective surgery of congenital cardiac shunts.<sup>7</sup> Vasodilator therapy is effective in a number of cases of primary plexogenic arteriopathy, especially in children. That it is not effective more often is understandable. In most patients with primary plexogenic arteriopathy obstructive intimal lesions, preventing or impeding dilatation, have developed by the time that the diagnosis is made.

How constriction of pulmonary arteries is brought about remains unsolved. So far attempts to identify the exact agents have had limited success. It is likely that hyperreactivity of pulmonary arteries, probably genetically determined, plays an important part in secondary as well as in primary plexogenic arteriopathy. A small percentage (1% or less) of individuals subjected to a certain stimulus – whether hepatic disease, or schistosomiasis, or anorectic drugs – develop plexogenic arteriopathy. It may be that such an individual variation in response is also present in experimental animals so that demonstration of the effect of any compound may be exceedingly difficult. Nevertheless there are strong indications that factors such as endothelium/smooth muscle interaction, shear stress, endothelial damage, and endothelium produced factors are involved in bringing about smooth muscle contraction.

The intimal proliferation and subsequent onion skin intimal fibrosis are likely to be a response to endothelial damage, constriction of the muscular coat, or both. They are not a consequence of thrombosis. Additional thrombotic lesions are common in adults with long-standing pulmonary hypertension of any cause; this is also true of adults with plexogenic arteriopathy.<sup>16</sup> In children with congenital heart disease or primary plexogenic arteriopathy intimal fibrosis is virtually limited to the concentric laminar type.

Fibrinoid necrosis, which occurs in small branches close to their origin from a larger artery – a site particularly exposed to haemodynamic forces – is closely related to the development of plexiform lesions. The plexiform lesion is found in the same location, while the wall of the branch around or adjacent to the lesion shows regular remnants of fibrinoid nec-

rosis and almost always destruction of part of the muscular coat or of its elastic laminae. The plexus itself consists of angioblastic tissue, proliferated within the fibrin clot in the lumen that usually accompanies the fibrinoid necrosis. The chance of fibrinoid necrosis and plexiform lesions developing is greater when the muscular coat of the artery has insufficiently increased in thickness. In other words, severe medial hypertrophy gives some protection to the development of plexiform lesions.<sup>29</sup>

#### Clinical significance and regression

The clinical consequences of plexogenic arteriopathy depend on the possibility of eliminating the cause and on the stage of the disease. In congenital heart disease, when normal haemodynamic conditions in the pulmonary circulation are restored by surgical intervention, both pulmonary hypertension and vascular disease may regress to normal. The same may also apply when anorectic drugs, as a cause of pulmonary hypertension, are withdrawn. In other situations the aetiological factors cannot be removed – either because an underlying process cannot be healed as in severe hepatic disease, or because they are unknown as in primary plexogenic arteriopathy.

When the cause is eliminated plexogenic arteriopathy will regress in its early stages,<sup>30</sup> but not when the disease has become too advanced. This could be seen when open lung biopsy samples were taken on a regular basis during surgical correction of a congenital cardiac shunt.<sup>31</sup> Two successive lung biopsy samples taken from the same patient during a banding procedure of the pulmonary artery and two or more years later during corrective surgery also provided essential information about the reversibility or irreversibility of the various lesions in the pulmonary arteries.<sup>32</sup>

It appeared that, under these circumstances, medial hypertrophy regressed – at least to some extent – and often completely. Cellular proliferation and mild to moderate fibrosis of the intima were reversible, although a remnant in the form of a thin layer of dense collagen-rich fibrous tissue could often still be recognised. On the other hand, when the concentric laminar intimal fibrosis was severe in the initial biopsy sample there was no regression. In these instances there appeared to be a progression so that fibrinoid necrosis and plexiform lesions, absent in the first biopsy, could be found in later material. As far as is known all the more severe arterial changes (dilatation lesions, fibrinoid necrosis, and plexiform lesions) carry a poor prognosis when found in biopsy material, particularly following corrective surgery. Such operations should be avoided if these lesions are present. An exception may well be the dilatation lesions provided no clusters have been formed.

There is therefore in the sequence of arterial lesions in plexogenic arteriopathy a point of no return when closure of a cardiac shunt, and thus removal of the cause of pulmonary hypertension, fails to induce regression of the vascular disease. This may explain why some

of the patients who developed pulmonary hypertension during the aminorex epidemic recovered upon withdrawal of the drug, while in others pulmonary hypertension increased and ran a fatal course. Furthermore, spontaneous closure of a ventricular septal defect may occur too late to prevent such a disastrous outcome.<sup>33</sup> It is even possible that in some instances this is basic to the development of primary pulmonary hypertension in children.

- 1 Heath D, Edwards JE. The pathology of hypertensive pulmonary vascular disease. A description of six grades of structural changes in the pulmonary arteries with special reference to congenital cardiac septal defects. *Circulation* 1958;18:533-47.
- 2 Wagenvoort CA, Nauta J, Van der Schaar PJ, Weeda HWH, Wagenvoort N. Effect of flow and pressure on pulmonary vessels. A semiquantitative study based on lung biopsies. *Circulation* 1967;35:1028-37.
- 3 Hatano S, Strasser T, eds. *Primary pulmonary hypertension*. Report on a WHO meeting. Geneva: World Health Organization, 1975.
- 4 Heath D, Wood EH, DuShane JW, Edwards JE. The structure of the pulmonary trunk at different ages and in cases of pulmonary hypertension and pulmonary stenosis. *J Pathol Bacteriol* 1959;77:443-56.
- 5 Wagenvoort CA. Vasoconstriction and medial hypertrophy in pulmonary hypertension. *Circulation* 1960;22:535-46.
- 6 Hall SM, Haworth SG. Onset and evolution of pulmonary vascular disease in young children: abnormal postnatal remodelling studied in lung biopsies. *J Pathol* 1992;166:183-93.
- 7 Del Nido PJ, Williams WG, Villamater J, Benson LN, Coles JG, Bohn D, et al. Changes in pericardial surface pressure during pulmonary hypertensive crises after cardiac surgery. *Circulation* 1987;76(Suppl III):93-101.
- 8 Meyrick B, Reid L. Ultrastructural findings in lung biopsy material from children with congenital heart defects. *Am J Pathol* 1980;101:527-42.
- 9 Wagenvoort CA, Keutel J, Mooi WJ, Wagenvoort N. Longitudinal smooth muscle in pulmonary arteries. Occurrence in congenital heart disease. *Virchows Arch (Pathol Anat)* 1984;404:265-74.
- 10 Heath D, Smith P. Electron microscopy of hypertensive pulmonary vascular disease. *Br J Dis Chest* 1983;77:1-13.
- 11 Heath D, Smith P, Gosney J, Mulcahy D, Fox K, Yacoub M, et al. The pathology of the early and late stages of primary pulmonary hypertension. *Br Heart J* 1987;58:204-13.
- 12 Heath D, Smith P, Gosney J. Ultrastructure of early plexogenic pulmonary arteriopathy. *Histopathology* 1988;12:41-52.
- 13 Bjornsson J, Edwards WD. Primary pulmonary hypertension: a histopathologic study of 80 cases. *Mayo Clin Proc* 1985;60:16-25.
- 14 Pietra GG, Edwards WD, Kay M, Rich S, Kermis J, Schloo B, et al. Histopathology of primary pulmonary hypertension: a qualitative and quantitative study of pulmonary blood vessels from 58 patients in the National Heart, Lung and Blood Institute Primary Pulmonary Hypertension Registry. *Circulation* 1989;80:1198-206.
- 15 Palevsky HI, Schloo BL, Pietra GG, Weber KT, Janicki JS, Rubin E, et al. Primary pulmonary hypertension: vascular structure, morphometry and responsiveness to vasodilator agents. *Circulation* 1989;80:1207-21.
- 16 Wagenvoort CA, Mulder PGH. Thrombotic lesions in primary plexogenic arteriopathy. Similar pathogenesis or complication? *Chest* 1993;103:844-9.
- 17 Wagenvoort CA, Dingemans KP, Vuzevski VD. Morphology of pulmonary vasoconstriction and vasodilation. In: Vincent JL, ed. *Yearbook of intensive care and emergency medicine*. Berlin: Springer Verlag, 1992:214-32.
- 18 Heath D, Smith P. The electron microscopy of "fibrinoid necrosis" in pulmonary arteries. *Thorax* 1978;33:579-95.
- 19 Yaginuma G, Mohri H, Takahashi T. Distribution of arterial lesions and collateral pathways in the pulmonary hypertension of congenital heart disease: a computer-aided reconstruction study. *Thorax* 1990;45:586-90.
- 20 Wagenvoort CA. The morphology of certain vascular lesions in pulmonary hypertension. *J Pathol Bacteriol* 1959;78:503-11.
- 21 Smith P, Heath D. Electron microscopy of the plexiform lesion. *Thorax* 1979;34:177-86.
- 22 Virmani R, Robinowitz M, McAllister HA. Primary pulmonary hypertension: quantitation of the size of plexiform lesions with uniformity in size irrespective of age. *Lab Invest* 1980;42:157-8.
- 23 Edwards WD, Edwards JE. Hypertensive pulmonary vascular disease in transposition of the great arteries. *Am J Cardiol* 1978;41:921-4.
- 24 Yamaki S, Horiuchi T, Sekino Y. Quantitative analysis of pulmonary vascular disease in simple cardiac anomalies with the Down syndrome. *Am J Cardiol* 1983;51:1502-6.
- 25 Clapp S, Perry BL, Farooki ZQ, Jackson WL, Karpawich PP, Hakimi M, et al. Down's syndrome, complete atrioventricular canal and pulmonary vascular obstructive disease. *J Thorac Cardiovasc Surg* 1990;100:115-21.
- 26 Heath D, Donald DE, Edwards JE. Pulmonary vascular changes in a dog after aorto-pulmonary anastomosis for four years. *Br Heart J* 1959;21:187-96.
- 27 Edwards BS, Weir EK, Edwards WD, Ludwig J, Dykowski RK, Edwards JE. Coexistent pulmonary and portal hypertension: morphologic and clinical features. *J Am Coll Cardiol* 1987;10:1233-8.
- 28 Mette SA, Palevsky HJ, Pietra GG, Williams TM, Bruder E, Prestipino AJ, et al. Primary pulmonary hypertension in association with human immunodeficiency virus infection. A possible etiology for some forms of hypertensive pulmonary arteriopathy. *Am Rev Respir Dis* 1992;145:1196-200.
- 29 Yamaki S, Wagenvoort CA. Plexogenic pulmonary arteriopathy. Significance of medial thickness with respect to advanced pulmonary vascular lesions. *Am J Pathol* 1981;105:70-5.
- 30 Heath D, Helmholtz HF, Burchell HB, DuShane JW, Kirklín JW, Edwards JE. Relation between structural changes in the small pulmonary arteries and the immediate reversibility of pulmonary hypertension following closure of ventricular and atrial septal defects. *Circulation* 1958;18:1167-74.
- 31 Wagenvoort CA. Open lung biopsies in congenital heart disease for evaluation of pulmonary vascular disease. Predictive value with regard to corrective operability. *Histopathology* 1985;9:417-36.
- 32 Wagenvoort CA, Wagenvoort N, Draulans-Noe Y. Reversibility of plexogenic pulmonary arteriopathy following banding of the pulmonary artery. *J Thorac Cardiovasc Surg* 1984;87:876-86.
- 33 Shemtov A, Fine LG, Rotem Y, Neufeld HN. Occlusive pulmonary vascular disease in a child with a spontaneously closed ventricular septal defect. *Isr J Med Sci* 1973;9:469-76.