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The Pathology of Pulmonary Veno-Occlusive Disease

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Summary. The histopathology of the lungs is described in 13 patients with pulmonary veno-occlusive disease. The patients were mostly children or young adults and there was no sex preference as is seen in primary pulmonary hypertension.

Characteristically the small pulmonary veins and venules were narrowed or occluded by intimal fibrosis, but larger veins were also affected. These obstructive lesions almost certainly resulted from organization of thrombi. Changes in the pulmonary arteries were generally secondary to obstruction of pulmonary venous flow but there was also a high incidence of thrombotic changes in the arteries.

Pulmonary parenchymal lesions commonly found included interstitial pneumonia and fibrosis, siderosis and cellular proliferation, together with increased activity of bronchial mucous glands and bronchial epithelial mucous cells. These changes may have indicated an infection, possibly of viral nature, as an aetiological factor in some of the patients. Consistent with such a cause is the common observation of an infectious febrile respiratory illness preceding the onset of symptoms due to pulmonary veno-occlusive disease.

Key words: Pulmonary Veno-Occlusive Disease — Pulmonary Venous Lesions — Pulmonary Arterial Lesions — Interstitial Pulmonary Fibrosis — Interstitial Pneumonia.

Veno-occlusive disease of the lung is a rare condition of uncertain origin. Until recently only very few cases had been reported but in the last few years an increasing number of cases have been published. An attempt to direct the attention of pathologists to the morphological changes in the lungs and its vessels in this unusual disease seems therefore warranted.

To the clinician pulmonary veno-occlusive disease may simulate primary pulmonary hypertension. The latter condition, however, affects principally the pulmonary arteries and not the veins. In pulmonary veno-occlusive disease there is a gradual narrowing and obstruction of the veins, particularly the pulmonary venules; whereas arterial changes, if present, are usually regarded as being secondary in nature.

The pathologist may overlook or misinterpret the vascular alterations and in some instances the veins and venules in the histological sections may resemble arteries so that the case may be regarded wrongly as one of pulmonary arterial hypertension. Sometimes the vascular lesions are restricted to small venules so that they remain unnoticed if the histological sections are not carefully studied.

We have had an opportunity to study lung tissue from 13 cases with pulmonary veno-occlusive disease and both the vascular and pulmonary parenchymal lesions will be described in detail.

Material and Methods

Lung tissue obtained at autopsy from 13 patients was collected by, or submitted to us, for study. Six of the cases have been published previously as single case reports.

In 4 cases stained histological sections were submitted to us, but in the remainder histological sections were cut at 7 μm from formalin fixed and paraffin embedded material and stained with haematoxylin and eosin, Lawson's elastic stain counterstained with Van Gieson's stain and Perl's iron stain.

In 5 cases uninterrupted serial sections were made in order to trace the origin of the vessels. In this way, when doubt arose about the nature of a vessel, identification of it either as an artery or a vein was possible by following its connection to a larger and readily recognizable vessel. Also the extension of the lesions within the affected vessels was studied in this way.

In all cases the sections stained for elastic tissue were used for morphometric assessment of the medial and intimal thickness of both pulmonary arteries and veins. The thickness of the media was measured and expressed as a percentage of the external vascular diameter (Wagenvoort, 1960) and the mean of 50 arteries and 50 veins was calculated in each case. The intimal thickness was expressed as a percentage of the internal vascular diameter (Wagenvoort and Wagenvoort, 1965) and calculated for the same numbers of vessels in each case.

Results

For the sex, age and some clinical details of the 13 patients, reference should be made to Table 1. The *main pathological findings* were confined to the heart-lung specimens. At autopsy, congestion of the liver and/or other organs was noted in all cases, and pleural effusions in two cases. Right ventricular hypertrophy was a constant finding. In one infant aged 8 weeks there was a subacute myocarditis but otherwise no essential alterations were found in the hearts. Arteries and veins in organs other than the lungs were not involved.

Macroscopically, the lungs almost without exception were firm and heavy with congested areas and often showed haemorrhages. On microscopical examination

Table 1. Sex, age, duration of symptoms and thickness of media and intima of both pulmonary arteries and veins in 13 patients with pulmonary veno-occlusive disease. Medial thickness is expressed as percentage of external vascular diameter, intimal thickness as percentage of internal diameter. Averages of 50 arteries and 50 veins

Case no.	Sex	Age (years)	Duration symptoms (years)	Pulm. arteries		Pulm. veins	
				media %	intima %	media %	intima %
1	♂	16	9/12	7.2	28.1	2.8	34.7
2	♀	45	7	7.0	19.5	4.4	26.8
3	♀	9	1	15.6	1.1	4.9	39.0
4	♀	12	9/12	12.4	9.2	4.3	57.5
5	♀	13	9/12	6.2	11.8	5.0	13.0
6	♀	13	7/12	6.2	27.8	5.0	41.2
7	♂	8/52	7/52	21.5	0	4.9	24.4
8	♂	3/12	2/12	22.1	0	6.9	60.9
9	♀	4	6/12	14.7	0	4.5	81.9
10	♀	6	1	8.7	0	4.6	23.9
11	♂	41	$1^1/_2$	8.2	28.7	4.1	59.5
12	♂	1	8/12	18.5	0	6.0	30.4
13	♂	33	?	9.8	3.4	5.0	42.0

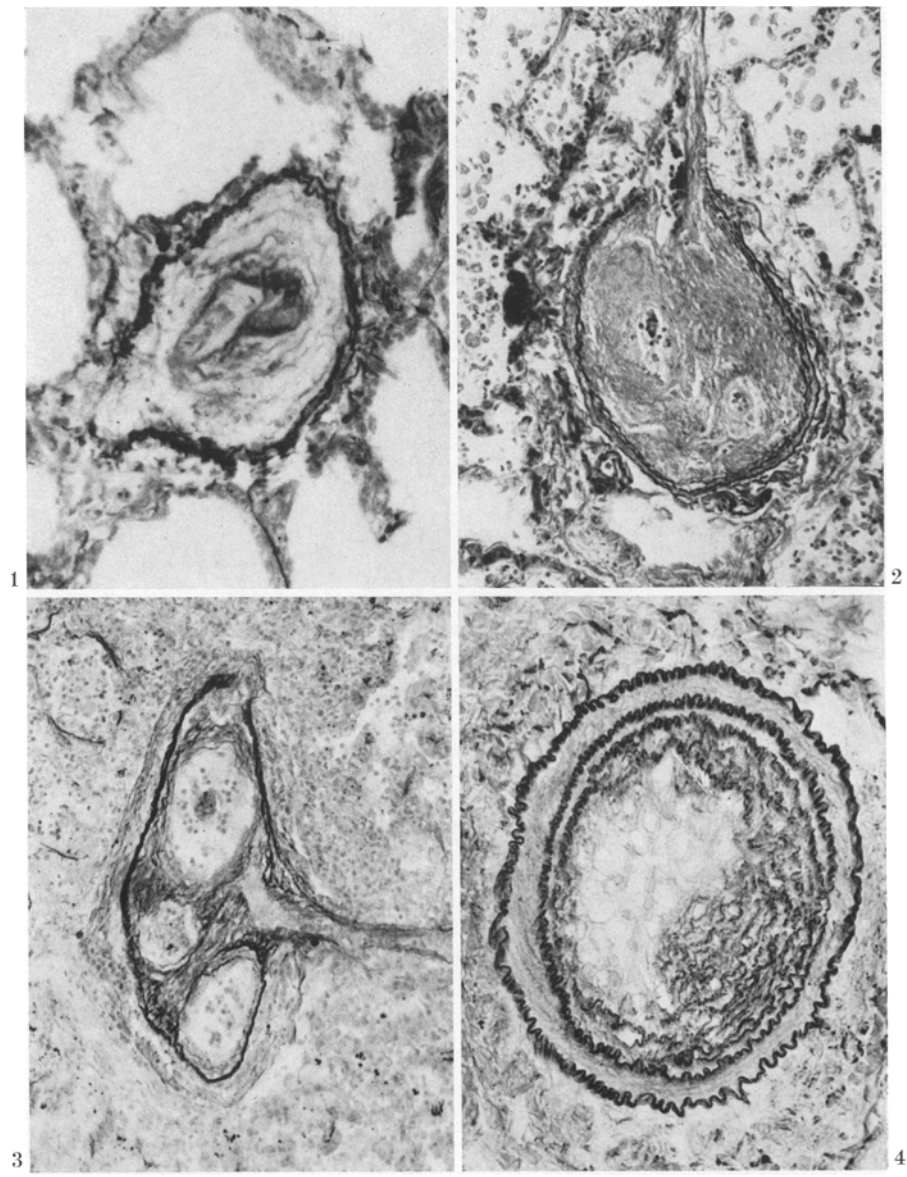

Fig. 1. Pulmonary venule in a woman aged 45 years with pulmonary veno-occlusive disease (P.V.O.D.). There is subtotal obliteration by loose, oedematous connective tissue (Elastic-van Gieson stain, × 140)

Fig. 2. Pulmonary venule in a girl aged 4 years with P.V.O.D. There is subtotal obliteration by dense collagen-rich fibrous tissue (El. v. G., × 140)

Fig. 3. Pulmonary vein in a male infant aged 8 weeks with P.V.O.D. Intraluminal fibrous septa divide the lumen in several compartments (El. v. G., × 140)

Fig. 4. Pulmonary venule in a male infant aged 3 months with P.V.O.D. Hypertrophy and marked arterialization of the media in addition to fibrous narrowing of the lumen. The vein simulates an artery (El. v. G., × 350)

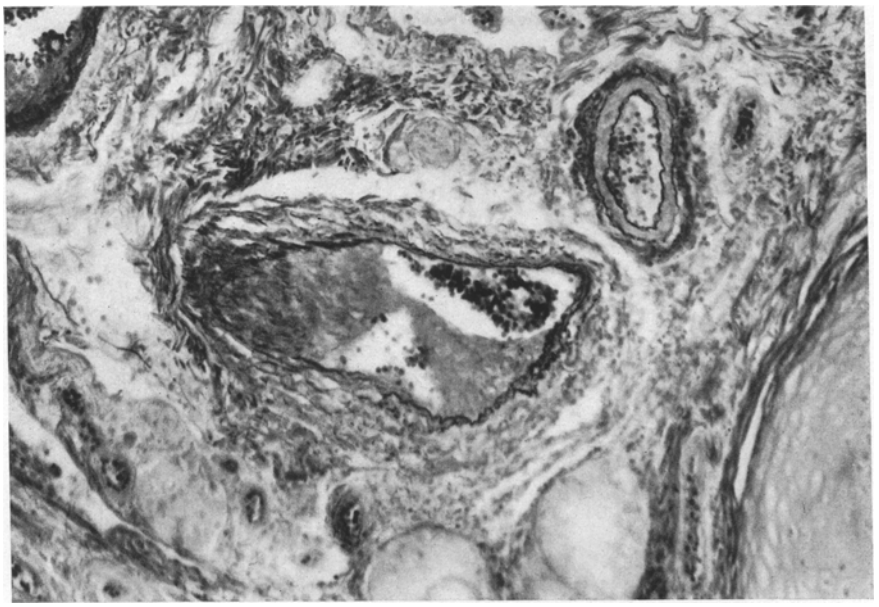

Fig. 5. Bronchial vein in a male infant aged 8 weeks with P.V.O.D. There is fibrotic obstruction and recanalisation (El. v. G., × 140)

all cases shared pronounced changes both in the blood vessels and in the pulmonary parenchyma.

Numerous pulmonary veins and venules were narrowed by intimal fibrosis even to the extent that they were completely or almost completely obliterated. The proportion of veins and venules affected varied between 30 and 90 per cent in our cases. In most the venous changes were equally and evenly distributed in both lungs. In a few cases, however, the veins in some parts of the lungs were much more affected than in others, but there was no constant preference for certain topographical areas. In two patients venous involvement was particularly striking in the upper lobes, including the lingula, while in 2 others the main changes were present in the lower lobes, the upper lobes being hardly affected.

In 4 cases the obliteration of the veins was produced by loose, oedematous connective tissue (Fig. 1), in four others the fibrosis was more dense with a great amount of collagenous and elastic fibres (Fig. 2). In the remaining patients there was an intermediate picture or a combination of both types.

Recognizable thrombi showing recent or early organization, were found in 3 cases. Intraluminal fibrous septa suggestive of recanalised thrombi (Fig. 3) were present in 11 cases.

The media of the veins was of approximately normal thickness in most instances but, particularly in the presence of dense collagen-rich fibrosis, it often showed hypertrophy and arterialization so that a striking resemblance of these veins to pulmonary arteries resulted (Fig. 4). The average thickness of the media and of the intima in 50 pulmonary veins and venules is given in Table 1.

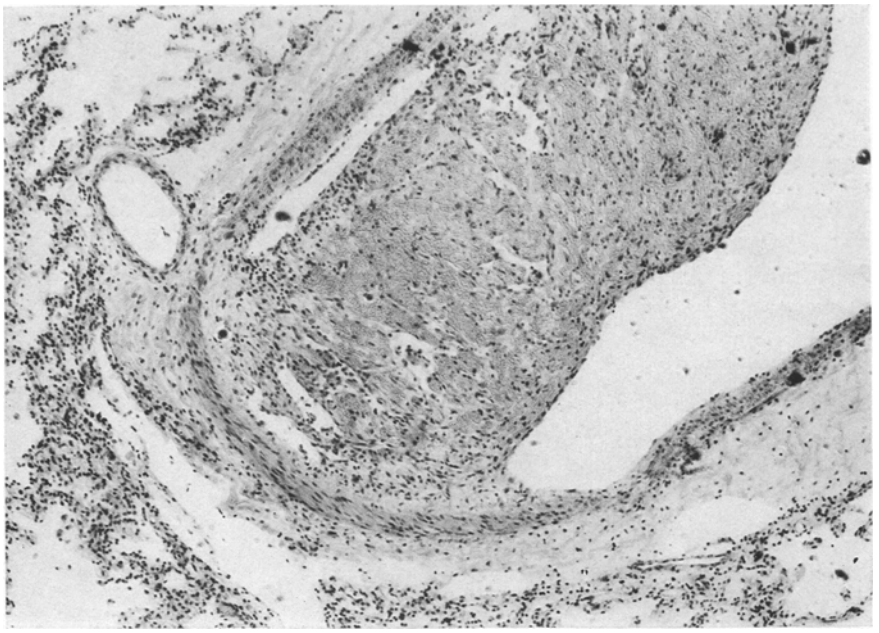

Fig. 6. Pulmonary artery with partly organized thrombus in the lumen in a girl aged 13 years with P.V.O.D. (Haematoxylin and eosin, × 60)

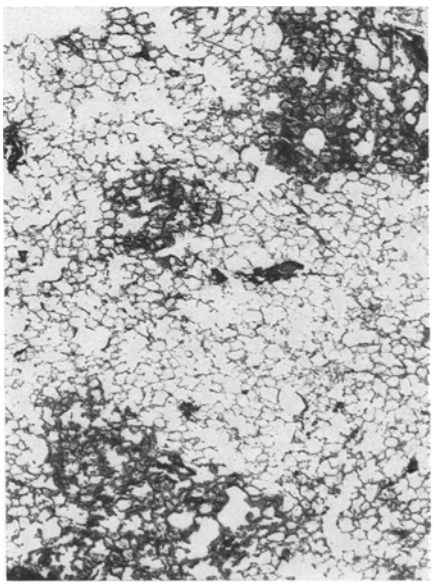

Fig. 7

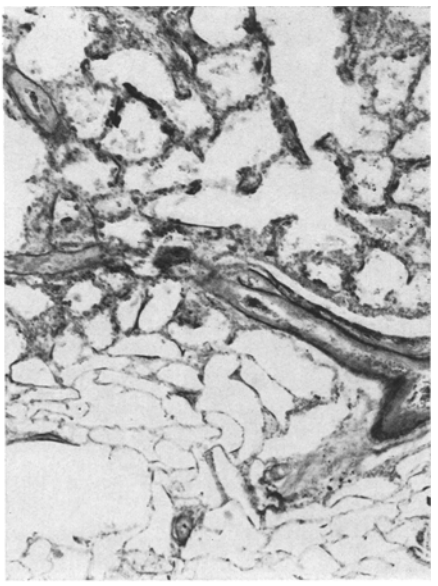

Fig. 8

Fig. 7. Multiple nodular areas of interstitial fibrosis and pneumonia in a youth aged 16 years with P.V.O.D. (H. and E., × 10)

Fig. 8. Area of interstitial fibrosis surrounded by partly obliterated venules in a girl aged 13 years with P.V.O.D. (El.v.G., × 60)

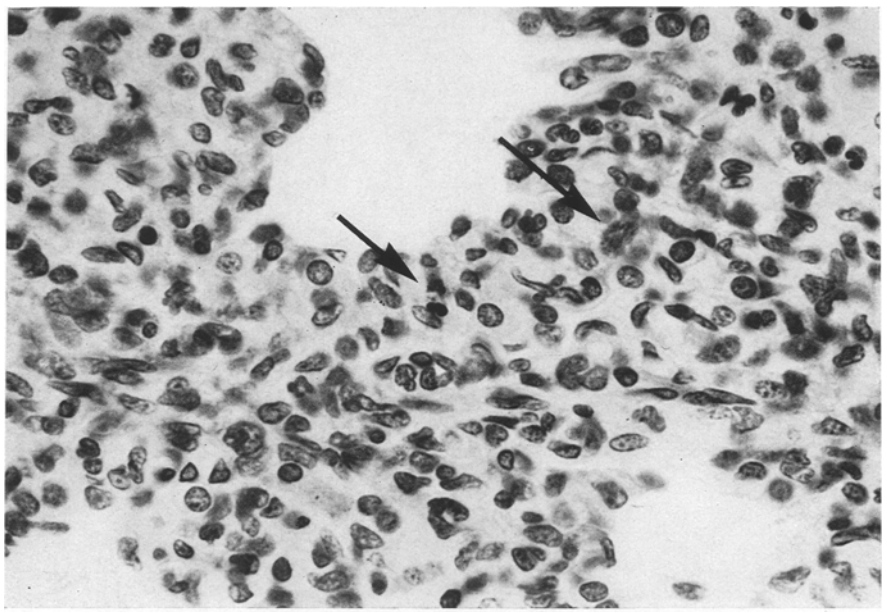

Fig. 9. Lung tissue with mitotic activity (arrows) and mononuclear infiltration of thickened alveolar walls in a male infant aged 3 months with P.V.O.D. (H. and E., × 500)

While medium-sized and small veins were particularly affected, the larger veins were not exempt. Such large veins, even in the hilar region, were affected with patchy intimal fibrosis and intraluminal fibrous septa in 7 patients.

Bronchial veins in the walls of the larger bronchi, and anastomoses between these and the pulmonary veins as traced in serial sections, were regularly involved (Fig. 5). The pulmonary lymphatics were dilated in most cases.

As compared with the pulmonary veins, the pulmonary arteries were less strikingly involved, but they were seldom completely normal. Medial hypertrophy though usually mild, was present in most patients. In 3 infants with pulmonary veno-occlusive disease, arterial medial hypertrophy was very severe. For the average medial thickness in each case reference should be made to Table 1.

Intimal fibrosis of pulmonary arteries varied greatly (Table 1), and in some instances even in various lobes of the same lung. It was never of the concentric-laminar type, as seen for instance in primary pulmonary hypertension, but was always patchy or crescent-shaped suggestive of an organised thrombus. Recognizable thrombi in arterial lumens occurred in 5 patients (Fig. 6). Fibrinoid necrosis, arteritis or plexiform lesions were absent.

The lung tissue usually showed some pulmonary oedema and congestion and often contained areas of haemorrhage. Characteristically there were small nodular areas of congested and thickened alveolar walls scattered through the lung tissue (Fig. 7), with deposition of collagen fibres in the affected walls which proceeded to distinct interstitial fibrosis. Haemorrhage was often present in and around these areas together with siderotic change. Siderotic changes were either minimal or so

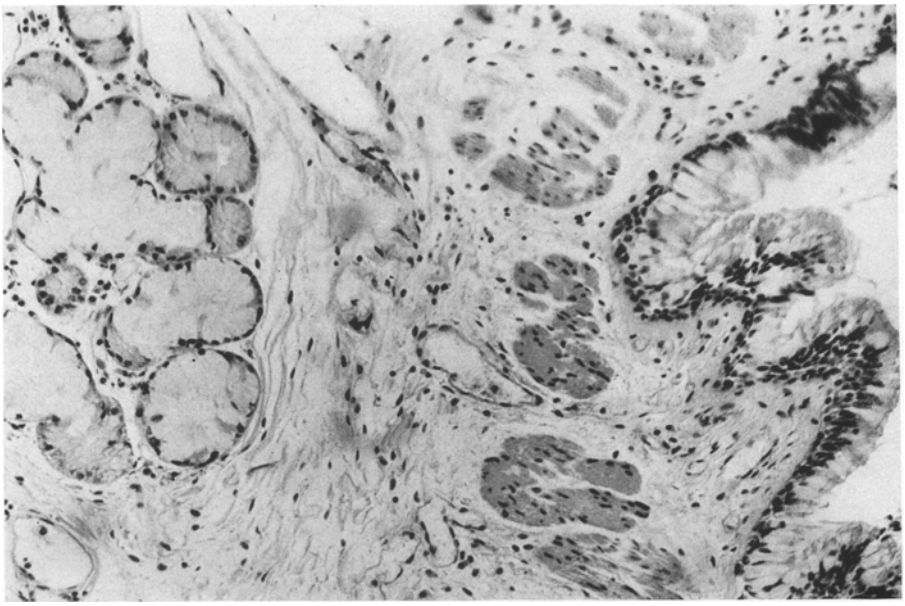

Fig. 10. Part of bronchial wall with hyperplasia and increased activity of mucous glands and of goblet cells in epithelial layer in a girl aged 13 years with P.V.O.D. (H. and E., × 140)

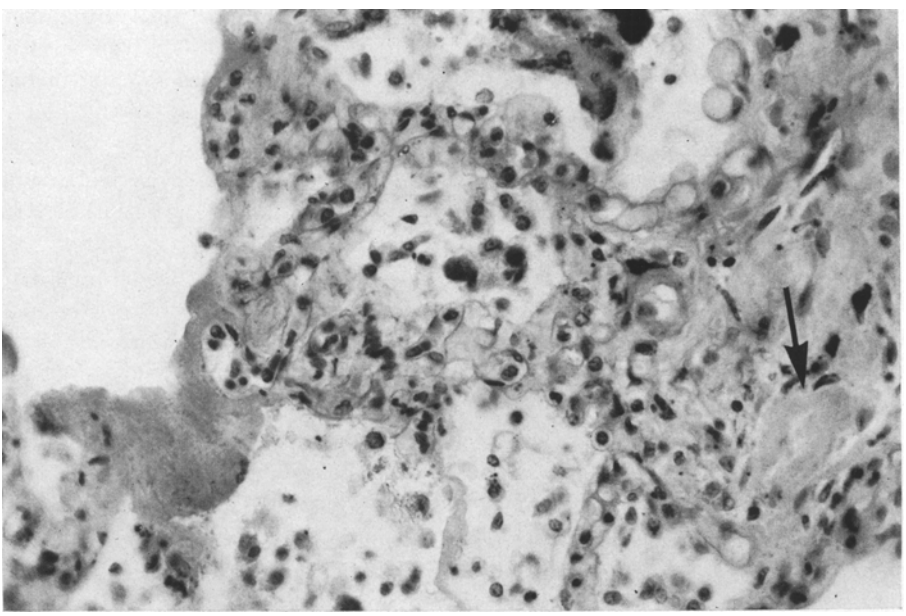

Fig. 11. Lung tissue with hyaline membranes, thickening of alveolar walls with some cellular infiltration, haemosiderin containing macrophages and one obliterated venule (arrow) in a girl aged 9 years with P.V.O.D. (H. and E., × 350)

pronounced that in one case a mistaken diagnosis of primary pulmonary haemosiderosis had been made.

Obstructed pulmonary veins and venules were often found lying within or just around the nodules of interstitial fibrosis (Fig. 8). In several instances these nodules coalesced to form large areas involving whole lobes or even whole lungs. In two infants cellular proliferation in the thickened alveolar walls was accompanied by considerable mitotic activity (Fig. 9).

An interesting and possibly significant observation was the presence of an inflammatory mononuclear exudate, sometimes with admixture of polymorphonuclear cells, within the alveolar walls in 9 of the 13 patients. This interstitial pneumonia was limited to areas of congestion and interstitial fibrosis. In 8 patients there was, in addition to mild degrees of chronic bronchitis, hyperplasia and increased activity of bronchial mucous glands or of the goblet cells in the bronchial epithelial lining (Fig. 10). In one case, a girl aged 9 years, hyaline membranes were present on the walls of respiratory bronchioles (Fig. 11).

Discussion

Obstruction of pulmonary venules and veins in the absence of cardiac disease such as mitral valve lesions is the hallmark of pulmonary veno-occlusive disease. Since Höra described a case in 1934, the condition has only rarely been diagnosed. In 1972 we described the morphological differences between primary pulmonary hypertension and pulmonary veno-occlusive disease (Wagenvoort, 1972), and we then collected 11 acceptable cases from the literature (Höra, 1934; Mallory, 1937; Brewer and Humphreys, 1960; Crane and Grimes, 1960; Bürki, 1963; Stovin and Mitchinson, 1965; Brown and Harrison, 1966; Heath *et al.*, 1966; Weisser *et al.*, 1967; Tingelstad *et al.*, 1969; Wagenvoort *et al.*, 1971). This list did not include 16 cases, briefly mentioned by Liebow *et al.* (1967) and Carrington and Liebow (1970).

Since that time 5 more cases have been published (Dainauskas *et al.*, 1971; Heath *et al.*, 1971; Liu and Sackler, 1972; Braun *et al.*, 1973; Rosenthal *et al.*, 1973).

Whether the recent rise in the number of case reports reflects an actual greater frequency of the condition or merely an increased interest resulting in more accurate diagnosis by both clinicians and pathologists remains uncertain.

Pulmonary veno-occlusive disease is rarely diagnosed during life and then usually by lung biopsy (Brown and Harrison, 1966). This was so in one of our own cases, a male infant aged three months. In this case, a sibling brother of the patient had died from the same disease 2 years before (Wagenvoort *et al.*, 1971) and thus the clinicians were already aware of the possibility of the diagnosis.

It has been pointed out by Carrington and Liebow (1970) that the wedge pressure is often normal or only slightly elevated so that it may not help in distinguishing the condition from primary pulmonary hypertension. They explained the relatively low wedge pressure in these cases on the basis of partial obstruction of small venules leading to a gradually diminishing pressure in the capillaries after the arterial inflow has been interrupted by the catheter.

Brown and Harrison (1966) suggested a similar mechanism. In their patient, flushing the catheter with saline solution, produced marked elevation of pressure with subsequently a slow fall to a low level.

As in primary pulmonary hypertension, children and young adults are predominantly affected. The two infants mentioned above are the youngest cases on record; while the cases described by Heath *et al.* (1966) and Höra (1934), were aged respectively 45 and 48 years and were the oldest.

There is no sex difference as in primary pulmonary hypertension, where, at least among adult cases, females are 4 times more often affected than males (Wagenvoort and Wagenvoort, 1970). Of the 23 patients with pulmonary veno-occlusive disease, reported either previously or included in our present material, 12 were males and 11 females. However, in the group of children 15 years or younger, the ratio was 6 to 9.

Among the morphological lesions in the lungs, the obstruction of the pulmonary venules and veins was responsible for the elevation of pulmonary arterial pressure and cor pulmonale with consequent pulmonary arterial changes.

It has been assumed by most authors that the venous obstruction results from thrombosis with subsequent organisation and often recanalisation. Recent formed thrombi may also be present (Carrington and Liebow, 1970). Our material confirmed the impression that the venous lesions were thrombotic in origin. In most cases, the venous obstructive changes strongly suggested organised or recanalised thrombi, while recent thrombi with or without early organisation were also sometimes present. Pulmonary phlebitis as described by Braun *et al.* (1973) was absent in our cases.

The medial hypertrophy and arterialisation of the media of pulmonary venules and medium-sized veins seen in some of our cases may have resulted from obstruction at a more distal level (Wagenvoort, 1970), and in this respect even the large pulmonary veins, sometimes at the hilar region, were often involved and narrowed by patches of intimal fibrosis or by intraluminal fibrous septa.

The pulmonary arterial lesions were probably secondary to the venous obstruction, although the high incidence of thrombotic lesions in pulmonary arteries in some of our cases was striking.

While the pathogenesis of the venous changes seems explicable on the basis of thrombus formation, the aetology remains obscure. Liu and Sackler (1972) suggested that addiction to sniffing powdered cleanser might have been a causative factor in their patient but no history of sniffing or inhaling drugs or other substances could be obtained in other cases.

Ingestion of drugs or toxic compounds has also been considered, since Crotalaria alkaloids found to be present in so-called "bush-tea" have been demonstrated to induce veno-occlusive disease of the liver in the West-Indies (Bras *et al.*, 1957). So far, however, there has been no indication that such substances were involved in any of the patients described with veno-occlusive disease of the lungs.

In previous reports (Brewer and Humphreys, 1960; Crane and Grimes, 1960; Tingelstad *et al.*, 1969; Carrington and Liebow, 1970; Heath *et al.*, 1971; Wagenvoort, 1972) a preceeding febrile, sometimes influenza-like illness occurred in patients with pulmonary veno-occlusive disease and this also applied to 5 of the patients in the present series. In addition, in one of our infants the mother had

suffered from such an illness in the 35th week of pregnancy (Wagenvoort *et al.*, 1971). Stovin and Mitchinson (1965) suggested that toxoplasmosis might be responsible but the antibody titres found in their case were not convincing.

The hypothesis that an infectious agent, possibly a virus, is involved in producing pulmonary veno-occlusive disease, is supported by our own material. The occurrence of interstitial pneumonia in 9 of our cases, and of bronchial mucous gland or mucous cell hyperplasia in 8 cases would be consistent with such a cause. Also supporting this view was the presence in one case, a girl of 9 years, of hyaline membranes in the lungs and in one infant aged 8 weeks of a simultaneous subacute myocarditis. It is assumed that a virus acts simultaneously both on the lung parenchyma and on the pulmonary vasculature, particularly the small pulmonary veins. In an Annotation (1972) it was pointed out that because pulmonary venous endothelium contains less plasminogen activator than systemic or pulmonary arterial endothelium, a toxic or infectious agent might, by attacking these cells, inhibit lysis and encourage thrombosis selectively in the veins.

In our cases in which the lungs were not uniformly affected, a fairly close topographical relationship existed between the interstitial pulmonary alterations and the occlusion of pulmonary veins and venules. Carrington and Liebow (1970) rejected an interstitial pneumonia in favour of chronic congestion as the cause for the interstitial fibrosis, on the basis of the marked siderosis in these areas. However, siderosis is likely to occur anyway in the presence of venous obstruction and thus cannot be used as an argument in deciding how interstitial fibrosis was brought about.

Although in our opinion there is strong support for a viral aetiology of veno-occlusive disease, in a number of the cases described, it cannot be overlooked that so far in no case has a virus been demonstrated by serological or other means. It also is uncertain whether the aetiology of pulmonary veno-occlusive disease is the same in all patients. For this reason in future cases it will be extremely important that attention should be paid to the presence or history of recent infections, contact with drugs or other substances and to the microbiological and serological data.

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