Familial Primary Pulmonary Hypertension

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Primary pulmonary hypertension or, as Evans, Short, and Bedford (1957) have termed it, solitary pulmonary hypertension, was first described by Clarke *et al.* (1927). In this paper the authors noted that the disease was more common in women and suggested the possibility of familial incidence in certain cases. With the development of cardiac catheterization and its associated techniques the number of reported cases has increased. In the majority of these there is no evidence of a familial incidence, but the original suggestion made by Clarke *et al.* has been borne out by a number of case reports in which primary pulmonary hypertension has been present in a number of related patients. Dresdale, Michtom, and Schultz (1954) reported primary pulmonary hypertension in two sisters and the son of one of them. Cahen *et al.* (1961) reported the disease in a mother and her daughter, and Van Bogaert *et al.* (1961) reported a brother and sister who died with signs of primary pulmonary hypertension. In the last instance the parents and two sibs were normal. Boiteau and Libanoff (1963) have described primary pulmonary hypertension in two sisters.

In this paper we describe a mother and two daughters, all of whom suffered from primary pulmonary hypertension. In all these cases the pathological changes were similar. In one, cardiac catheterization was performed.

CLINICAL DATA

The family history is shown in Table I. The age at death of the grandparents makes it unlikely that either suffered from primary pulmonary hypertension. Their elder daughter (M. J. W.) died at the age of 30 and was believed to have had heart disease. No post-mortem record is available for her, but it is not unlikely that she suffered from primary pulmonary hypertension. Her

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son, aged 34, is well. The second daughter (F. E. W.) is the mother in the series reported here. She died, aged 49, of pulmonary hypertension, and two daughters (G. N. and T. C.) were found at necropsy to have had the same disease. Her two sons are well without symptoms. There is a fourth generation, daughter of G. N., who is alive and well aged 4 years.

Mother (F.E.W.) She was first seen in hospital in 1956, aged 44, complaining of frequency and stress incontinence. Heart and lungs were clinically normal. In 1959 she was seen again. She complained that she had increasing dyspnoea with ankle oedema for the past 3 years. The blood pressure was 110/80 mm. Hg. There was a loud systolic mitral murmur with a thrill; the second pulmonary sound was loud and split; there was evidence of right-sided cardiac failure, the liver being large and tender. Moderate clubbing of the fingers was present, but there was no definite central cyanosis. Investigations showed a normal blood urea; haemoglobin was 10.7 g./100 ml.; chest radiograph showed cardiac enlargement with congestion at the lung bases. She was treated for her cardiac failure with digoxin and diuretics, and improved considerably. One year later she was admitted again in gross right-sided heart failure; blood pressure was 100/50 mm. Hg. The second pulmonary sound was noted to be very accentuated. She did not respond to treatment and died shortly after admission.

Daughter (T.C.) This girl was well, apart from minor ailments, until 1958 when she presented with a history of increasing tiredness for five months. She had lost 26 lb. (11.8 kg.) in weight during this time, and for the eight days preceding admission to hospital she had noticed a stabbing pain in the left side of the chest of pleuritic type. Examination revealed a 23-year-old woman with normal heart sounds. Blood pressure was 140/80 mm. Hg. Radiology showed slight cardiac enlargement with a little pulmonary congestion. Her pain was thought to be related to muscular strain due to her work as a garage hand. She had recurrent nose bleeding during 1960 and 1961, and in November 1961, when in late pregnancy, she was found to have a loud pulmonary second sound. Her bleeding tendency was

TABLE I

FAMILY HISTORY

investigated with negative results. Two months later, when she was in her 36th week of pregnancy she was admitted to the maternity unit in gross cardiac failure and died within a few hours.

Daughter (G.N.). This 25-year-old woman presented in 1962, complaining of increasing shortness of breath, which dated from the birth of her daughter two years earlier. She could walk at a steady pace on the level but climbed stairs or hills only with difficulty. There was no history of ankle oedema. On examination she was a healthy-looking girl with no cyanosis or clubbing. There was no engorgement of the neck veins. Blood pressure was 110/70 mm. Hg. There was no oedema of the ankles or sacrum. The apex beat was not displaced and was right ventricular in type. The second pulmonary sound was loud, palpable, and closely split. There was a grade I systolic murmur best heard at the second and third left intercostal spaces. The respiratory system and alimentary system were normal.

Investigations. Hæmoglobin 14 g./100 ml.; white cell count 9,600. Serum electrolytes were within normal limits. Chest radiography showed that the heart was slightly enlarged in its transverse diameter; the pulmonary conus was prominent. Electrocardiogram indicated right ventricular hypertrophy and strain. Cardiac catheterization showed pulmonary hypertension. The pressure in the main pulmonary artery was 90/30 mm. Hg and the pressure in the right ventricle was 90/0 mm. Hg. Oximetry showed a low cardiac output with no evidence of a shunt. Dye curves were normal. The patient's condition deteriorated rapidly with increasing dyspnoea and she died of congestive cardiac failure.

Findings at Necropsy. All three patients showed similar post-mortem changes. There was gross hypertrophy and dilatation of the right ventricle of the heart, dilatation of the right atrium, and incompetence of the tricuspid valve. Back pressure changes were evident in the liver, spleen, and kidneys. The lungs showed oedema and terminal tracheobronchitis. There was oedema of the legs. No recognizable congenital abnormalities were found on naked eye examination. Apart from gross cyanosis, the unborn 36-week female infant of the daughter (T.C.) appeared to be normal.

Histological Examination. All three patients showed similar histological changes in the lungs.

Larger pulmonary arteries. Intimal proliferation, reduplication, and splitting of elastic laminae, with thickening of the muscle layers and patchy fibrosis, were present (Fig. 1). Some very large arteries showed atheroma.

Medium-sized pulmonary arteries. Intimal proliferation, usually with vacuolation, and moderate hypertrophy of the muscle layers, was found. The degree of intimal proliferation varied, being most marked where the vessel branched (Fig. 2), though some muscular arteries were completely occluded by intima (Fig. 3).

Arterioles. Intimal proliferation was present, sometimes associated with a fibrinoid necrosis of the deeper parts (Fig. 4). The proliferated endothelium was either recanalized or had grown in such a manner as to leave sinusoids in the polypoid proliferation (Fig. 5). In some instances this produced a resemblance to a glomerulus (Fig. 6). These polypoid endothelial glomeruloid lesions were usually peri-bronchial in distribution and were adjacent to, or surrounded by, a

FIG. 1.—Hypertensive degeneration of the pulmonary artery (F.E.W.). (Verhoeff van Gieson. $\times 180$.)

FIG. 3.—Intimal obliteration of muscular artery (T.C.). (Verhoeff van Gieson. $\times 180$.)

FIG. 2.—Intimal proliferation with vacuolation in muscular pulmonary artery (F.E.W.). (Verhoeff van Gieson. $\times 194$.)

FIG. 4.—Canalized intimal proliferation with basal degeneration (G.N.). (Verhoeff van Gieson. $\times 180$.)

FIG. 5.—Glomeruloid lesion (G.N.). (Verhoeff van Gieson. $\times 180$.)

large number of dilated blood-filled capillaries. The glomeruloid lesions were most frequently found in vascular channels devoid of both muscle and elastic tissue, and in this respect they resembled dilated capillaries. A continuity between an arteriole and a glomeruloid can be found in several sections. Fig. 7 shows the continuity between fibrinoid intimal change and canalized endothelial proliferation.

No histological abnormality was detected in the lungs of the unborn female child.

DISCUSSION

Primary pulmonary hypertension occurring in a mother and two daughters is described. It is likely that the mother's sister also died of pulmonary hypertension. The male members of the family (Table I) appear to have escaped the disease. This exclusive incidence in the female members of the family suggests that the disease may be genetically determined by a dominant sex-linked gene. However, Yu (1958), who reported 6 cases from his own experience and collected published reports of 55 others, noted an 80 per cent incidence in females. In the 14 reported to have a familial incidence

(Table II) there were 12 females to 2 males. This is sufficiently close to an 80 per cent female incidence to make it probable that the findings in our family were due to chance.

The measurements of pulmonary artery pressure have been shown to be of prognostic value. Nielsen and Fabricius (1961) investigated 14 cases of primary pulmonary hypertension and found that a pressure of 70 mm. Hg in the pulmonary artery was compatible with an average survival of three and a half years, while an increase in pressure to over 70 mm. Hg was compatible with survival for only two and a half years. Our experience supports this prognostication. Our third patient (G.N.) died 14 months after a pulmonary artery pressure of 90/30 mm. Hg was recorded.

The pathology of the vessels in primary pulmonary vascular sclerosis has been reviewed by Brenner (1935). He reported on 36 male and 32 female cases, mostly occurring in childhood, adolescence, and early adult life. The right ventricle was hypertrophied and dilated; the larger pulmonary arteries were normal or showed atheromatous change, but the main changes were to be found in the smaller pulmonary arteries, where there was often

FIG. 6.—Glomeruloid lesion (F.E.W.). (Verhoeff van Gieson. $\times 180$.)

FIG. 7.—Glomeruloid lesion in continuity with fibrinoid degeneration in small vessel (T.C.). (Verhoeff van Gieson $\times 180$.)

medial hypertrophy or patchy fibrosis of the muscular layers. The smallest arteries showed a proliferation of the intima which may completely occlude the vessel. Similar changes occurred in our patients.

The curious lesion resembling a glomerulus (Fig. 6 and 7) appears to have some relationship to congenital heart disease. The lesion is found in a small artery as a glomerulus-like body with multiple channels which lead into a cluster of very delicate thin-walled vessels which in turn lead into pulmonary capillaries. Wagenvoort (1959) described such lesions in the smaller vessels of 10 patients with

pulmonary hypertension. In 9 of them the pulmonary hypertension was due to intracardiac shunts, but the tenth had primary pulmonary hypertension, and in this patient the greatest number of glomeruloid lesions was found. Similar lesions have been described in 14 of 21 patients by Rich (1948), who thought they were recanalized organized thromboses. Hufner and McNicol (1958) described extreme endothelial proliferation and arterial occlusion, and found that distal to the occlusive process the elastic lamina disappeared completely, the media became thinner, and the vessel showed a second type of

TABLE II
REPORTED CASES OF FAMILIAL PRIMARY PULMONARY HYPERTENSION

Author	No. of Cases	Relationship
Clarke <i>et al.</i> (1927)	2	Sisters
Dresdale <i>et al.</i> (1954)	3 (?4)	Mother, son, and daughter (? Mother's brother)
Van Bogaert <i>et al.</i> (1961)	2	Brother and sister
Cahen <i>et al.</i> (1961)	2	Mother and daughter
Boiteau and Libanoff (1963)	2	Sisters
Present series	3 (?4)	Mother and 2 daughters (? Mother's sister)
Total	14	Males 2 Females 12

occlusive proliferation of endothelial cells which they called "glomoid". These lesions were associated with an angiomatous formation of thin-walled vessels and were always peribronchial in location. Our cases showed similar histological findings. There was pulmonary atheroma, intimal proliferation, medial hypertrophy, and fibrosis and glomerular bodies in thin-walled peribronchial vessels. These findings were not present in the stillborn infant of one of our patients (T.C.). These lesions do not occur in the pulmonary hypertension of mitral stenosis or pulmonary embolism; they are found in cases of pulmonary stenosis (Rich, 1948) and are, therefore, not likely to be due to the hypertension. Their relation to primary pulmonary hypertension is at present obscure, but if further observation confirms that they are frequently associated with this condition it may give some lead to the nature of the disorder.

Theories of the aetiology of primary pulmonary hypertension have been reviewed by Farrar (1963). The pressures in the pulmonary artery and the aorta before birth are approximately equal and the vessels are histologically similar. Farrar concludes that the weight of the evidence available is in favour of an acquired aetiology for primary pulmonary hypertension. Only greatly extended observations will permit a firm conclusion at this point, and there remain many patients in whom it is difficult to avoid suspecting that the condition is congenital in origin.

SUMMARY

Primary pulmonary hypertension occurring in a mother and two daughters is reported. The published cases are reviewed. The pathological changes in the lung do not differ from those found in the non-familial cases of idiopathic pulmonary hypertension.

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ADDENDUM

Our attention has been drawn to a further description of familial primary pulmonary hypertension. The authors describe three cases, sibs, in whom the diagnosis was established at necropsy.

REFERENCE

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