

Primary Pulmonary Hypertension: Familial Occurrence*

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Primary pulmonary hypertension was defined by Brenner in 1935 as being characterized by "sclerosis of the pulmonary arteries for no obvious reason (such as cardiac or pulmonary disease) as well as hypertrophy of the right but not the left side of the heart" (Brenner, 1935). All the earlier cases were diagnosed at necropsy, and the condition was regarded as rare. In recent years the introduction of cardiac catheterization, together with a better appreciation of the clinical picture caused by the disease, has led to the diagnosis of the condition in life and to the further analysis of its causes.

Two disorders of the pulmonary arteries may be responsible for causing "primary pulmonary hypertension" as defined by Brenner, namely primary or essential pulmonary hypertension, and recurrent and cumulative pulmonary embolism (packed pulmonary emboli). These two diseases may be exceedingly difficult to differentiate from each other both clinically and pathologically (Owen *et al.*, 1953). The clinical syndromes may in fact be identical. The pathological features are often distinctive, however, and the two conditions can usually be differentiated in the absence of macroscopical and microscopical evidence of past or present pulmonary emboli, and by angiographic studies after death.

A number of reports indicate that primary pulmonary hypertension may occur in families (Dresdale, Michtom, and Schultz, 1954; Van Epps, 1957; Schaffner, 1958; Coleman, Edmunds, and Tregillus, 1959; Husson and Wyatt, 1959; Fleming, 1960; Cahen *et al.*, 1961; van Bogaert *et al.*, 1961; Boiteau and Libanoff, 1963; Melmon and Braunwald, 1963; Parry and Verel, 1966; Rogge, Mishkin, and Genovese, 1966; Kingdon *et al.*, 1966). The

present paper presents three cases of primary pulmonary hypertension occurring in all the female members of one family in one generation. In two, sections of the lungs and other tissues obtained at necropsy were available for examination.

CASE REPORTS

Case 1. A 36-year-old woman (IV. 18) was admitted to St. Thomas' Hospital in February 1960, complaining of shortness of breath on exertion. One and a half years previously she had a normal pregnancy. After delivery she noted the onset of fatigue and shortness of breath. Her exercise tolerance gradually became limited by these complaints, and five months before admission she had the first of several syncopal attacks, when, after climbing a hill, she lost consciousness and was incontinent. She also complained of a non-productive cough and palpitations, but she had no angina. Previously she had one other normal pregnancy and one miscarriage. Labile systemic hypertension was noted in 1955.

On physical examination the pulse was 90 and regular; the blood pressure was 105/90 mm. Hg. There was peripheral cyanosis, and clubbing was absent. The jugular venous pressure was raised. Examination of the heart revealed a loud systolic murmur maximal between the apex beat and the left sternal edge. There was no diastolic murmur or gallop; the pulmonary second sound was loud; the lungs were normal; the liver and spleen were not felt; and there was no oedema. The neurological examination was normal.

The chest x-ray examination showed enlargement of the pulmonary artery (Fig. 1). The electrocardiogram showed right axis deviation, right ventricular hypertrophy, with T wave inversion over the entire praecordium, and tall P waves.

While awaiting cardiac catheterization, she developed bilateral calf tenderness, and thrombophlebitis was diagnosed; anticoagulants were begun. Two weeks after admission she experienced left pleuritic chest pain, and bilateral superficial femoral vein ligation was performed. Her condition deteriorated, and she developed increasing cyanosis, weight gain, and an enlarging liver,

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together with periodic fever spikes up to 38.9–39.4°C. (102–103°F.). Three blood cultures were negative. Digitalis, diuretics, oxygen, and antibiotics were given. She became increasingly drowsy and hypotensive, and died on the 47th hospital day.

At necropsy the heart showed considerable right ventricular hypertrophy, but the valves and septa were normal. The lungs were normal except for slight thickening of the larger branches of the pulmonary artery. Post-mortem angiograms showed a failure of the terminal branches throughout the pulmonary arterial tree to fill with the injection material (Fig. 2). Macroscopically no recent emboli, thrombi, or infarcts were found. The liver and spleen were enlarged due to chronic congestion, but no phlebothrombosis was noted in the superficial or deep leg veins.

The most striking microscopical changes were found in the muscular branches of the pulmonary arteries, vessels ranging between 500–100 μ in diameter. The walls of these arteries showed concentrically arranged cellular, intimal, fibro-elastoid thickening, which largely accounted for the increase in mural width of such vessels (Fig. 3). Outside the thickened intima the medial muscle was visible in some instances, but had almost totally disappeared in others. In some of the muscular arteries the intimal tissue had undergone partial hyaline change. As a result of the intimal thickening the lumens were considerably reduced in diameter,

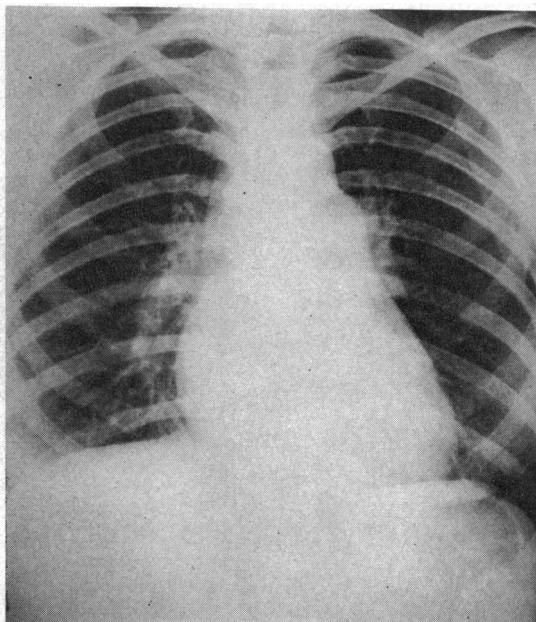


FIG. 1.—Chest x-ray film from Case 1 showing enlargement of the pulmonary arterial segment.

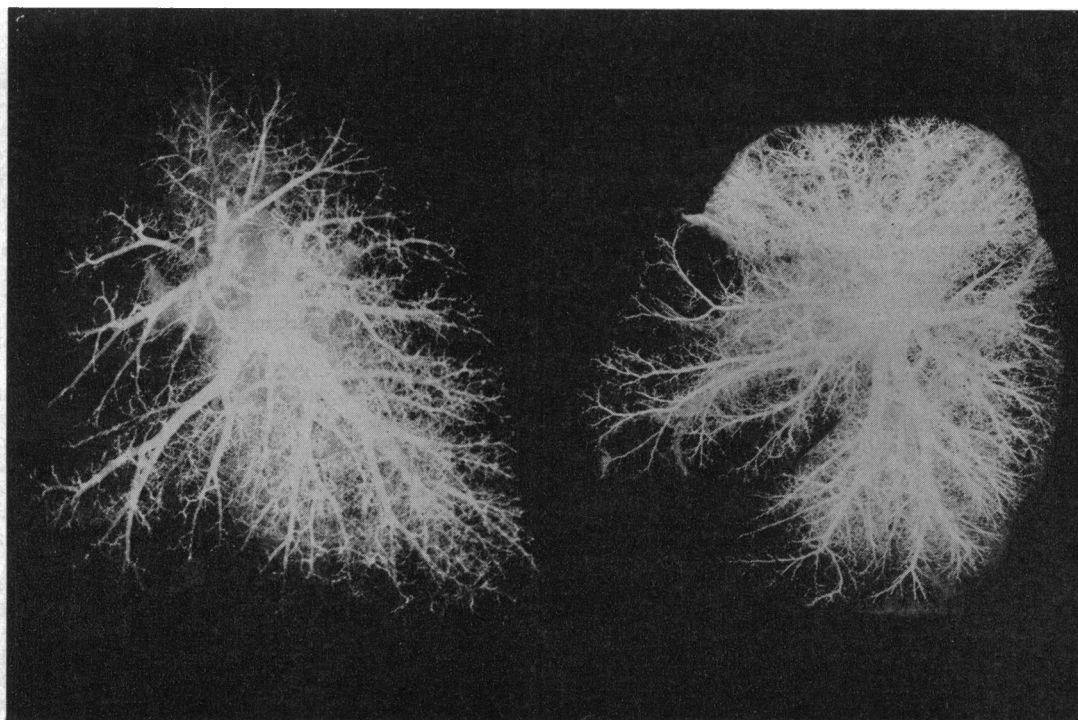


FIG. 2.—Post-mortem pulmonary angiograms. *Left*—lung from Case 1: note the failure of the finest branches to fill with contrast material throughout the lung; the main and segmental branches of the pulmonary artery are dilated. *Right*—normal lung for comparison.

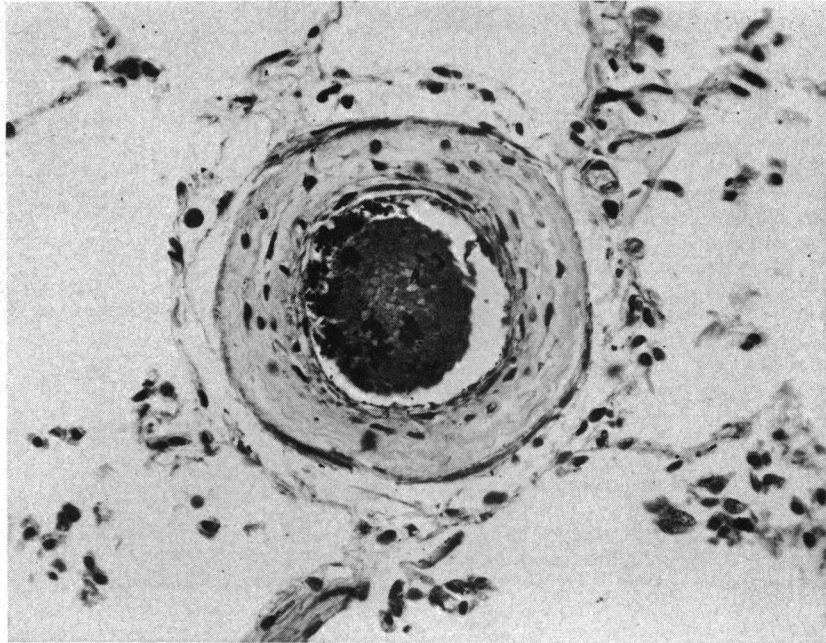


FIG. 3.—Section of lung from Case 1 ($\times 140$). The vessel is distended by contrast material (visible as black particles in the lumen).

and this accounted for the failure of such vessels to fill adequately in the angiograms. In the large elastic vessels the media was moderately hypertrophied, and intimal atheromatous plaques were present. The smallest muscular branches of the pulmonary artery and the arterioles showed little abnormality.

No identifiable recent or organizing thrombotic embolus was found in the many sections of lung that were examined, and the concentric pattern of the intimal fibro-elastosis led to the conclusion that the change was probably not due to thromboembolism.

Case 2. A 27-year-old woman (IV. 20) was admitted to St. Thomas' Hospital in February 1961, complaining of shortness of breath on exertion and fainting spells. Six months previously, and two months after a normal pregnancy, she noted dyspnoea on exertion and fatigue. This rapidly became more severe and she became breathless with slight exertion. Three months before admission she had a syncopal attack and was incontinent; one further syncopal attack occurred later. She also noted praecordial pain on exertion, and developed a cough productive of small amounts of whitish sputum. In the past she had pneumonia at the age of 2, and attacks of asthma and frequent chest colds up to the age of 15. Thereafter she enjoyed perfect health until in 1955, and again in March of 1960, she suffered mild attacks of bronchitis.

On physical examination the pulse was 106 and regular; the blood pressure was 80/60 mm. Hg. There was peripheral cyanosis, and slight clubbing. The jugular

venous pressure was not raised. Examination of the heart showed a soft systolic murmur over the third and fourth interspaces at the left sternal edge. The pulmonary second sound was loud. No diastolic murmur was heard. The lungs were normal. The liver was just palpable, but the spleen was not felt. There was no oedema, and the neurological examination was normal.

Laboratory tests showed a haemoglobin of 16.2 g. No lupus erythematosus cells were seen, and the latex test was negative. The chest x-ray film showed an enlarged pulmonary artery. The electrocardiogram showed a vertical electrical axis and borderline right ventricular hypertrophy. The results of cardiac catheterization are shown in Table I.

In hospital the patient had a single syncopal attack following a warm bath. She was started on anticoagulants and sent home. One month later her condition was unchanged except for the presence of left calf tenderness and left leg swelling. While at home she experienced a sudden urge to defaecate, collapsed, and died. No necropsy was performed.

Case 3. A 12-year-old schoolgirl (IV. 19) was admitted to University College Hospital in January 1929, complaining of breathlessness and fainting attacks. At the age of 6, while recovering from scarlet fever, she had noted the onset of mild breathlessness. One year before admission the breathlessness became more marked, and was accompanied by an intractable dry cough. She was noted to be cyanosed. Four months before admission she began to have syncopal attacks, and for three months

before admission she was confined to bed with breathlessness and oedema of the legs. In the past she had pneumonia at the age of 3.

On physical examination the pulse was 115 and regular. There was cyanosis and clubbing. Examination of the heart revealed "systolic and diastolic murmurs in the mitral area," and there was a gallop rhythm. Râles and dullness were noted at the right lung base. The liver was enlarged to the umbilicus, and ascites and oedema of the flanks and legs were present.

No x-ray film or electrocardiographic studies were available.

The patient was treated for congestive heart failure with paracentesis and Southey's tubes, oxygen, digitalis, venesection, and application of leeches. In spite of these measures her condition deteriorated, and terminally she developed a rapid pulse, was very cyanosed and tachypnoeic, and became oliguric. She died after 50 days in hospital.

At necropsy there were ascites and bilateral pleural effusion, causing collapse of both lung bases. There was great dilatation and hypertrophy of the right ventricle, but the left ventricle was normal in size. The heart valves were normal, and no septal defects were found. The lungs were tough and indurated, and the pulmonary arteries were described as being "prominent and standing out as rigid gaping tubes." There were small fatty plaques in the intima of the large arteries. The liver showed severe venous congestion.

Due to the kindness of Sir Roy Cameron, we were able to re-examine the original sections of lung obtained *post mortem* from this patient 33 years previously. All

TABLE I

RESULTS OF CATHETERIZATION IN CASE 1

Pulmonary arterial pressure (mm. Hg)	105/53
Right brachial arterial pressure (mm. Hg)	130/98
Pulmonary capillary wedge pressure (mm. Hg)	6
Arterial oxygen saturation (%)	94
Cardiac output (l./min.)	2.0
Pulmonary vascular resistance (units)	30

the lung sections showed a cellular, concentric fibro-elastoid thickening of medium-sized muscular branches of the pulmonary arteries (Fig. 4). The muscular coat of these vessels was often not identifiable, and when present was atrophied. Similar changes also extended into the smaller muscular pulmonary arteries down to a diameter of 100 μ . There was also hypertrophy of the medial musculature in the large and medium-sized elastic branches, but there was no evidence of any recent or organizing thromboemboli. The changes were very similar to those found in Case 1.

DISCUSSION

These three cases followed a clinical course compatible with the diagnosis of primary pulmonary hypertension, and in two cases (Cases 1 and 3) the diagnosis was proven at necropsy. The history and clinical course in Case 2 bear such a close resemblance to the others that it seems probable that this patient died from the same cause.

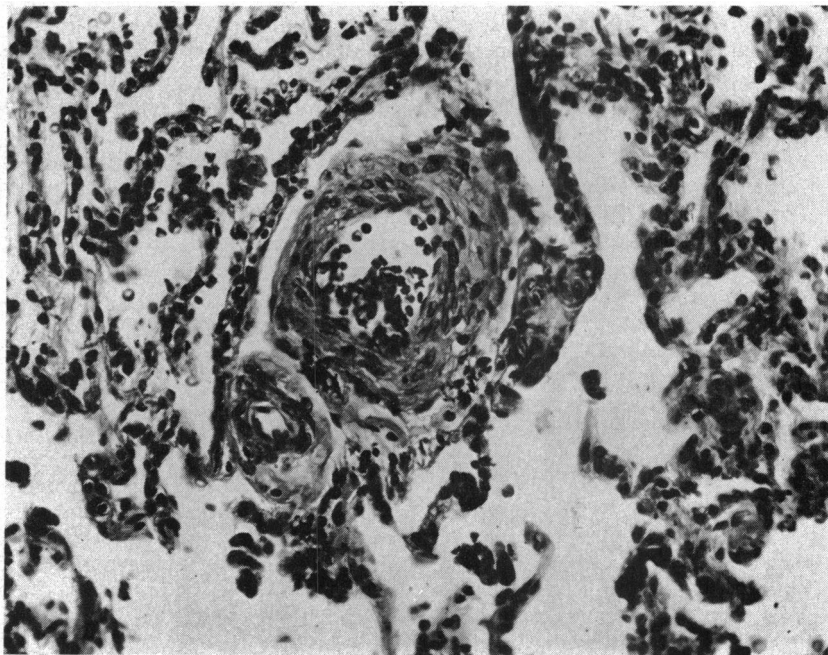


FIG. 4.—Section of lung from Case 3 ($\times 140$.)

Clinical Features. In Cases 1 and 2, symptoms first appeared shortly after pregnancy, and in all 3 patients death followed within 19 months of the onset of serious breathlessness. The published reports of proven cases of primary pulmonary hypertension show that it is more common in women, particularly young adults, and that it typically runs its malignant course within a few years. Appearance of symptoms during or shortly after pregnancy usually suggests thromboembolic disease (Wilcken, MacKenzie, and Goodwin, 1960), though proven primary pulmonary hypertension occurring in relation to pregnancy has been reported before (Dresdale, Schultz, and Michtom, 1951; Evans, Short, and Bedford, 1957), and appears to be common in familial cases (Coleman *et al.*, 1959; Parry and Verel, 1966; Rogge *et al.*, 1966; Kingdon *et al.*, 1966). In Case 3 the age of the patient supports the diagnosis of primary pulmonary hypertension, since this disease is known to occur in children (Berthrong and Cochran, 1955), whereas pulmonary embolism is rare.

The clinical syndrome of severe breathlessness, easy fatigability, and often angina pectoris and syncopal attacks, combined with physical, *x*-ray, and catheter findings indicative of pulmonary hypertension, but with absence of evidence of mitral valvular disease, primary lung disease, or right-to-left shunting, is characteristic of either primary pulmonary hypertension or multiple pulmonary embolism. Both diseases may occur either with or without clinical evidence of leg vein thrombophlebitis or pulmonary embolism. Because of these similarities the clear differentiation of primary pulmonary hypertension from multiple pulmonary embolism may sometimes be made only at necropsy.

Pathological Features. It is unlikely that packed and recurrent pulmonary emboli were responsible for pulmonary hypertension in Cases 1 and 3, because of the absence of any recent or organizing emboli in the pulmonary arterial tree, as judged by extensive microscopical examination. In these cases, the outstanding microscopical changes in the lungs were the even, concentric, intimal fibro-elastoid thickening seen in the smaller muscular branches of the pulmonary arteries, and the medial hypertrophy in the large proximally situated elastic arteries. These changes caused obstruction of the affected small vessels as shown in Fig. 2. This angiogram demonstrates that the small muscular branches of the pulmonary artery fail to fill throughout the lung, a finding that is more characteristic of primary pulmonary hypertension than of pulmonary embolism. Pulmonary emboli much more commonly lodge in the lower lobes of the lungs, and show a lesser

tendency to be distributed evenly throughout the lungs.

Functional vasoconstriction of the pulmonary muscular arteries may be regarded as the first recognizable stage in the genesis of primary pulmonary hypertension (Wade and Ball, 1957; Kuida *et al.*, 1957), and this at first may be overcome by the injection of drugs such as tolazoline hydrochloride ("priscol") and acetylcholine into the pulmonary artery (Dresdale *et al.*, 1954; Wood, 1958; Shepherd and Wood, 1959). In a few cases with clinical findings of primary pulmonary hypertension, necropsy has shown a paucity of vascular lesions (Evans *et al.*, 1957; De Navasquez, Forbes, and Holling, 1940; McGuire *et al.*, 1957). In such cases it may be presumed that death occurred before structural changes in the arteries took place; that is, vasoconstriction alone was responsible for pulmonary hypertension. In the majority of cases seen *post mortem*, however, structural lesions are present throughout the entire lung at necropsy, presumably as a consequence of prolonged and generalized vasospasm causing an increase in the pulmonary arterial pressure.

The microscopical lesion observed in these cases was a concentric fibro-elastoid intimal thickening, and this finding supports the diagnosis of primary pulmonary hypertension. The belief that this change follows prolonged pulmonary arterial vasoconstriction is based on the work of Barnard (1954), who showed that concentric intimal fibro-elastosis follows prolonged vasospasm in rabbits, and that this change contrasts with the more usual eccentric plaques of fibro-elastoid tissue resulting from intimal incorporation of pulmonary emboli.

Late in the course of primary pulmonary hypertension secondary phlebothrombosis in the leg veins may occur, as a sequel to diminished cardiac output and venous stasis, and can give rise to pulmonary emboli. Autochthonous thrombotic changes within the pulmonary arteries also commonly occur late in the course of the disease. In this advanced stage primary pulmonary hypertension may become pathologically indistinguishable from multiple pulmonary embolism.

Familial Features. We have been able to obtain information about 94 relatives of these three cases (Fig. 5), but no other occurrences of primary pulmonary hypertension were found. There are no known consanguineous marriages in this family. The data are complete for generations II and III, and for all members of the propositus' immediate family in generations IV and V.

Of the four male sibs of the propositus, one (IV. 17) died at the age of 5 days of unknown causes.

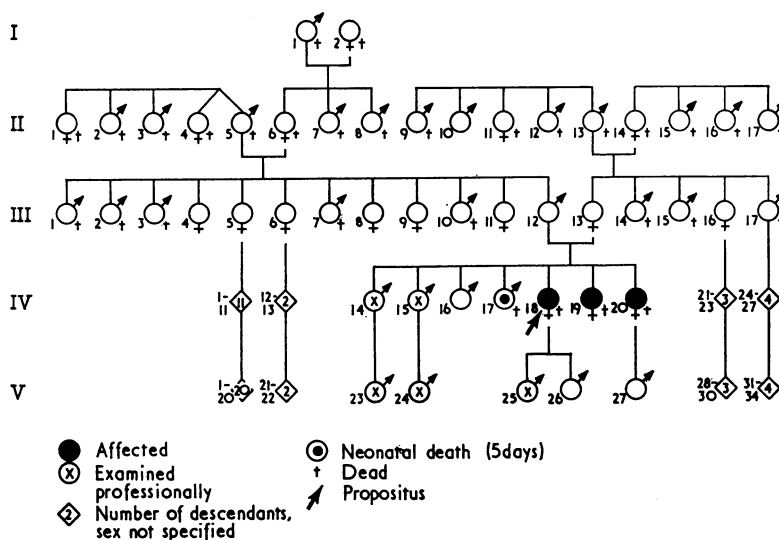


FIG. 5.—Pedigree of the family.

Two of the three living brothers (IV. 15 and 16), are in good health, but the third (IV. 14), age 46, has had phlebitis of the lower extremities, resulting in pulmonary embolism and infarction. He recovered completely, with no clinical or x-ray evidence of pulmonary hypertension. One of the two healthy brothers (IV. 15), and the three oldest male offspring of the next generation (V. 23, 24, and 25), who are 17, 11, and 14 years of age, respectively, were examined and chest x-ray films were found to be normal. The two youngest males (V. 26 and 27), ages 3 years and 9 months, respectively, are in good health, but there was no chest x-ray examination.

There is no evidence that members of this family have a high incidence of various congenital anomalies, as has been noted in other familial cases of primary pulmonary hypertension (Coleman *et al.*, 1959; Melmon and Braunwald, 1963).

A review of the published material indicates that familial primary pulmonary hypertension documented by catheterization, necropsy, or both, has been reported in 27 other cases in 12 families (Table II). In some of these families, and in a few other case reports, it has been suggested, but not conclusively demonstrated, that relatives of affected persons may have had the disease (Dresdale *et al.*, 1954; Fleming, 1960; Melmon and Braunwald, 1963; Clarke *et al.*, 1927; Taft and Mallory, 1946). It is possible that difficulties in diagnosis along with differences in age of onset may have concealed other familial cases.

In the present series of three cases the evidence strongly suggests that primary pulmonary hypertension occurred as an isolated finding in three sibs

of one generation. This genealogy is consistent with an autosomal recessive mode of inheritance, with incomplete penetrance in the male sibs. This family resembles others in which all cases occurred in one generation, but differs from those with more than one generation affected, in which a dominant mode of inheritance would be more likely (Table II).

Further differences appear to exist between cases of primary pulmonary hypertension occurring in a single generation and those in which more than one generation is affected (Table III). The incidence of the disease in cases thus far reported is much more equally distributed between the two sexes when only one generation is affected, and also symptoms appear at a younger age. This raises the possibility that two different pathological mechanisms are involved in the genesis of familial cases, the single generation cases perhaps representing a recessive and congenital disorder of the pulmonary vasculature, and the multiple generation cases perhaps being dominant and developing later in life. The pathological studies of Heath and Edwards (1960) support this concept. It is also noteworthy that in every family with disease in more than one generation, the phenomenon of genetic anticipation (Melmon and Braunwald, 1963) has been present, offspring being affected at an earlier age than parents (Table II). Thus the average age of parents is 46.9 years, and of offspring 21.9 years.

Familial Primary Pulmonary Hypertension—Clinical Implications. In some respects primary pulmonary hypertension resembles systemic essential

TABLE II
REPORTED CASES OF PRIMARY PULMONARY HYPERTENSION
OCCURRING IN FAMILIES

Reference	Age (yr.)	Sex	Relationship	Diagnosis at		Other cases in family probable
				Cath.	Necropsy	
Dresdale <i>et al.</i> (1954)	43	F	Mother	+		+
	21	M	Son	+		
Van Epps (1957)	6	M	Sibs	+	+	
	4	M				
Schaffner (1958)	56	F	Mother		+	
	31	F	Daughter		+	
Coleman <i>et al.</i> (1959)	22	F	Sibs		+	
	35	F				
	41	M				
Husson and Wyatt (1959)	4	M	Sibs		+	
	3	F				
Fleming (1960)	32	F	Mother	+		+
	10	F	Daughter	+		
Cahen <i>et al.</i> (1961)	46	F	Mother	+		
	20	F	Daughter		+	
van Bogaert <i>et al.</i> (1961)	12	F	Sibs	+	+	
	5	M				
Boiteau and Libanoff (1963) and Melmon and Braunwald (1963)	44	F	Sibs	+	+	+
	28	F				
Parry and Verel (1966)	47	F	Mother		+	
	23	F	Daughter		+	
	25	F	Daughter	+	+	
Rogge <i>et al.</i> (1966)	48	M	Father	+	+	
	18	F	Daughter		+	
Kingdon <i>et al.</i> (1966)	56	M	Father		+	
	22	F	Daughter	+	+	
	27	F	Daughter	+	+	
This series	36	F	Sibs		+	
	27	F				
	12	F				

hypertension, its counterpart in the systemic circulatory system, and a tendency to occur in families is one similarity. The disease is perhaps more closely analogous to malignant systemic hypertension because of its rapidly fatal course. It is likely, however, that in the early stages of primary pulmonary hypertension a clinically undetected increase in pulmonary arterial pressure may exist for some time, and that the abnormality goes undetected because no simple procedure exists for measurement

of pulmonary artery pressures. If any treatment, such as prolonged oxygen inhalation or infusion of pulmonary vasodepressors, were to be successful in the treatment of this disease, it should be most effective in early cases, before structural lesions are established.

Attention to the familial tendency may offer an opportunity of discovering early cases of primary pulmonary hypertension. Other members of the family of an affected person, particularly if female, should be examined at intervals for alteration in the pulmonary second sound or radiological evidence of change in size of the pulmonary artery, and should undergo catheterization if indications of the disease develop.

TABLE III

RATIO OF FEMALE/MALE CASES AND AVERAGE AGE ACCORDING TO NUMBER OF GENERATIONS AFFECTED*

	Multiple generations affected	Single generation affected
Sex ratio (female/male)	5.0	1.4
Average age (yr.)	33.2	17.3

* The two cases reported by Boiteau and Libanoff (1963) and Melmon and Braunwald (1963) are considered to have multiple generations affected.

SUMMARY

Three cases of primary pulmonary hypertension occurring in 2 women and a girl in one generation of one family are described. In 2 of them the diagnosis was confirmed and differentiated from

multiple pulmonary embolism at necropsy.

A survey of previously reported cases indicates that 27 other familial instances of primary pulmonary hypertension have been reported in 12 families. Certain distinctions are noted between families in which a single generation is affected and those where the disease occurs in multiple generations. The former were characterized by nearly equal sex distribution and early age of onset; the latter showed a preponderance of women, and occurred at a later age. These findings suggest that single generation cases may represent a congenital and recessive disorder of the pulmonary circulation, and multiple generation cases a dominant disorder which appears later in life.

It is also suggested that awareness of a familial tendency in this disease may lead to discovery, and possibly to more effective treatment of the malady at an early stage.

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