Familial pulmonary hypertension

Evidence of autosomal dominant inheritance

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A patient with primary pulmonary hypertension is the fourth member of a family proven to have the disease. The patient's father married twice; the disease appeared in both families, and was transmitted through two generations. Multiple genetic and environmental factors may result in pulmonary hypertension, but the distribution of cases in this family and in others reported is consistent with the autosomal dominant inheritance of a single genetic trait.

Since its documentation by Clarke *et al.* in 1927, there have been 13 reports of the familial occurrence of primary pulmonary hypertension (Rogge, Mishkin, and Genovese, 1966; Hood *et al.*, 1968). The mode of inheritance has not been defined because of difficulty in distinguishing primary pulmonary hypertension from pulmonary hypertension secondary to thromboembolic disease and other causes; thus, proven cases in more than one generation are rare. The largest family reported is that of Lange (1948) who found that 82 members of a family had a history of dyspnoea and cyanosis; 42 members were personally examined, and many were found to have the clinical features of pulmonary hypertension, but no catheterization studies were performed. No definite conclusion could be reached as to the mode of inheritance in the suspected cases. Melmon and Braunwald (1963) reconstructed an extensive pedigree of a family with two proven and three suspected cases; they concluded that the mode of inheritance was dominant. Hood *et al.* (1968) studied another family with three affected sisters and concluded that inheritance was autosomal recessive; they reviewed other published family trees and suggested that there might be two different modes of inheritance.

We have recently studied an affected member of the family reported by Fleming (1960), in which the father married twice. Appearance of the disease in both his families provides unique evidence of a dominant mode of inheritance.

Case report

The patient, aged 51, was admitted to Royal Melbourne Hospital in June 1969. For six months before admission he had noticed dyspnoea on exertion. There were no other symptoms, but he was apprehensive as he was aware of the family history (see later).

On physical examination there was a dominant 'a' wave in the jugular venous pulse. There was no right ventricular heave and no sign of right ventricular failure. A right atrial sound and accentuation of the pulmonary component of the second sound were noted and confirmed by phonocardiography. The electrocardiogram showed evidence of right atrial and right ventricular hypertrophy. A dominant main pulmonary artery and peripheral oligoemia were seen on chest x-ray.

Cardiac catheterization was performed under local anaesthesia with diazepam 15 mg. premedication. The right heart pressures before and after 100 per cent oxygen are summarized in the Table. Pulmonary wedge pressure was normal and dye dilution curves showed no evidence of a left-to-right or a right-to-left shunt. Pulmonary angiography confirmed the narrowing of the peripheral vessels, and there was no obstruction in the main pulmonary arteries.

Empirical treatment with phenindione resulted in slight symptomatic improvement over a follow-up period of six months.

Family tree The pedigree of the family is shown in the Fig.

The paternal grandmother (I.2) of the proband (III.5) had asthma and died at the age of 76 of 'natural causes'. His father (II.9) died of cancer aged 71. Three of his father's sibs had died suddenly and unexpectedly in childhood. He married twice, the first wife dying of pneumonia aged 32.

There were five offspring from the first marriage, including the proband who has four symptom-free children between the ages of 12

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TABLE Clinical and haemodynamic data on four cases of primary pulmonary hypertension

Subject	Age at first symptoms (yr.)	Symptoms	Jugular venous pulse	Right ventricular heave	Auscultation	Systemic blood pressure (mm. Hg)	Electrocardiogram	Chest x-ray	Pulmonary artery pressure (mm. Hg)		Pulmonary vascular resistance	Outcome
									At rest	After 100 per cent O ₂		
III.5	56	Exertional dyspnoea	'a' wave	—	Right atrial sound; accentuated P ₂	150/110	P pulmonale; right ventricular hypertrophy	Pulmonary trunk prominent; peripheral oligæmia	78/30	70/30	9 units	Alive 6 months after onset of symptoms
III.2	47	Exertional dyspnoea; wave ankle oedema	'a' wave	—	Right atrial sound	150/110	Right ventricular hypertrophy	Pulmonary trunk prominent	95/40	Not done	—	Died age 47
III.7	32	Chest pains; exertional dyspnoea	'a' wave	+	Ejection click; short pulmonary ejection bruit; accentuated P ₂	120/80	P pulmonale; partial RBBB	Pulmonary trunk prominent	105/55 (mean = 70)	Unchanged	32 units	Died age 33
IV.8	10	Frequent colds; syncope	'a' wave	+	Ejection click; short pulmonary ejection bruit; accentuated P ₂	120/75	P pulmonale; partial RBBB	Pulmonary trunk normal; peripheral oligæmia	55/30 (mean = 40)	45/25	11 units	Died age 15

and 21. They have no abnormality on physical examination by their own doctor; we have reviewed their electrocardiograms which are normal. A sister (III.2) was investigated at the Alfred Hospital, Melbourne, and was found to have primary pulmonary hypertension (see Table). She died, aged 47, and is survived by three children, one of whom has recurrent bronchitis. Another sister (III.4) is alive, aged 54; she has no abnormalities on physical examination by her own doctor, and we have reviewed the electrocardiogram which is normal. A brother (III.3) died from asthma at the age of 56. Another brother (III.1) is alive and well aged 61 and we have no clinical details.

There were four offspring from the second marriage. III.7 was found to have primary pulmonary hypertension on investigation at Royal Prince Alfred Hospital, Sydney (see Table), and she died at age 33. Her daughter (IV.8) was investigated at the same hospital and was also found to have the disease; she died at age 15. Two brothers of III.7 are alive and well, age 35 and 37; we have no further information. There is no evidence of consanguinity in the first or second marriage of II.9 the father of the propositus.

Discussion

An autosomal dominant mode of inheritance best accounts for the distribution of primary pulmonary hypertension in this family. The remarriage of the father with the appearance of the disease in both his families provides support for this. The great variation in the age at which symptoms develop suggests that there may be a subclinical form of the disease

consistent with longevity in some members of the family. This could explain the apparent absence of the disease in the father.

A recessive mode of inheritance is barely possible, as the gene would need to have been present in heterozygous form in the father, both wives, and again in the husband of III.7. There is no evidence of sex-linking as cases have occurred in both men and women.

A further alternative is that pulmonary hypertension in this family is not due to a single genetic abnormality, but, like systemic hypertension, is the expression of multiple genetic and environmental factors. A predisposition towards abnormal development of the lung may result in varying degrees of pulmonary hypertension or other abnormalities of the respiratory system. Thus, scattered cases of asthma appear in the present family tree (Fig.), and Melmon and Braunwald (1963) reported agenesis of one lung and hypoplasia of the other in an infant born to a woman with pulmonary hypertension.

A cousin of III.7 with indirect evidence of pulmonary hypertension was included in the pedigree of this family when reported by Fleming (1960). With this inclusion, a polygenic mode of inheritance must be invoked to explain the distribution of cases. However, the finding that a step-brother (III.5) has proven pulmonary hypertension suggests that the disease in this family is due to a single genetic trait transmitted by an autosomal dominant mode of inheritance.

In other families with the disease proven

in more than one generation, autosomal dominance best explains the distribution of cases (Dresdale, Michtom, and Schultz, 1954; Parry and Verel, 1966; Rogge *et al.*, 1966; Kingdon *et al.*, 1966).

In a large family reported by Melmon and Braunwald (1963) and Boiteau and Libanoff (1963) the diagnosis was proven by catheterization in only two sibs, but there was strong clinical and post-mortem evidence of the disease in a total of five cases in three generations and the distribution is best explained by a dominant mode of inheritance.

On the other hand, Hood *et al.* (1968) suggested that a recessive mode of inheritance best explained the distribution of cases in families in which only one generation was affected (Van Epps, 1957; Coleman, Edmunds, and Tregillus, 1959). Hood *et al.* (1968) reported a further case in which three sisters were affected and four brothers in the same generation were not. However, the parents were not examined; it is possible, as in the present family, that one parent was affected with a mild form of the disease. On this basis, the mode of inheritance could be interpreted as autosomal dominance with varying expression.

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FIG. Pedigree showing familial occurrence of primary pulmonary hypertension.

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Addendum

The 34-year-old daughter of III.2 noted dyspnoea on exertion in mid-1969. She had been a heavy smoker for 15 years and had symptoms of chronic bronchitis. The results of spirometry in September 1969 were FEV₁ 1.3 litres, vital capacity 2.7 litres (predicted 3 litres), ratio FEV₁/VC 48 per cent.

Cardiac catheterization on 11 March 1970 gave the following results: pulmonary artery pressure 28/11 (mean 20) mm.Hg at rest and 32/18 (mean 25) mm.Hg after exercise. Exercise was tolerated badly, causing severe breathlessness. There was hyperventilation with PCO₂ of 30 mm.Hg at rest and at exercise. The cause of the hyperventilation was not determined but a psychogenic cause was considered likely.

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