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Hypertrophic cardiomyopathy with unusual features in a family

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Seven out of 16 members of two generations of a family affected by a form of hypertrophic cardiomyopathy are described. The symptoms included recurrent exertional and recumbent chest pain and bouts of rapid palpitations. The physical signs included large jugular venous and apical 'a' waves, a systolic ejection murmur, and wide splitting of the second heart sound. The electrocardiogram was characterized by a short PR interval, increased QRS amplitude, and persistent ST depression. There was little or no cardiomegaly but some pulmonary artery prominence. There was no evidence of subaortic stenosis or coronary artery disease in three members who were catheterized, but mild infundibular pulmonary stenosis was found in two. Ischaemic heart disease was closely mimicked and it is suggested that some cases of angina with normal coronary arteriograms may represent a similar condition.

It is at present still uncertain whether several different types of familial cardiopathy exist or whether a single disorder appears in a variety of forms, of which obstructive hypertrophy is one (Nasser *et al.*, 1967).

The kindred described in this report presents an unusual but consistent combination of clinical features, some resembling familial hypertrophic obstructive heart disease (Brent *et al.*, 1960; Hollman *et al.*, 1960; Paré *et al.*, 1961; Horlick, Petkovich, and Bolton, 1966; Frank and Braunwald, 1968), and others resembling familial cardiomyopathy (Beasley, 1960; Battersby and Glenner, 1961; Whitfield, 1961; Barry and Hall, 1962; Bishop, Campbell, and Wyn Jones, 1962) or familial cardiomegaly (Evans, 1949; Gaunt and Lecutier, 1956; Campbell and Turner-Warwick, 1956; Soulié *et al.*, 1957; Walther, Madoff, and

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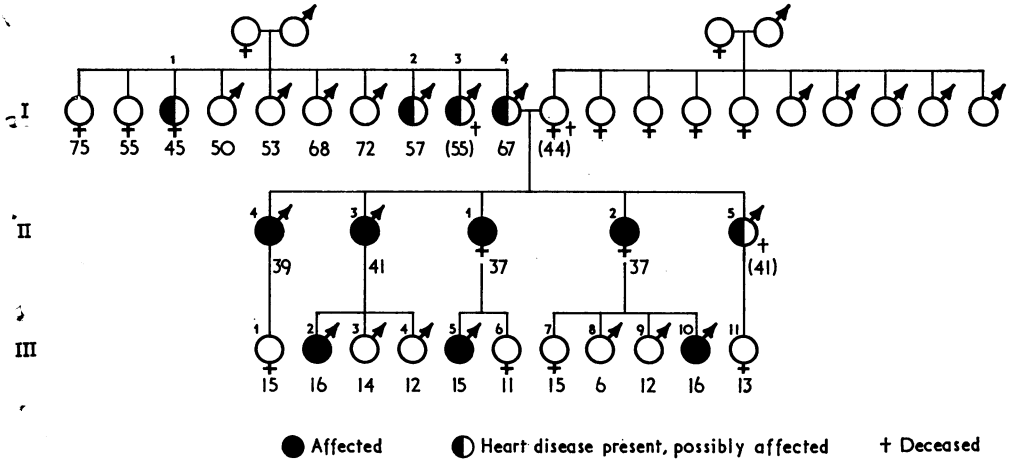
FIG. 1 *The family tree. The numbers above each symbol are the case numbers referred to in the text. The number below each symbol is the age of the subject in years. For deceased subjects the age at death is given in parenthesis.*



Zinner, 1960). In each symptomatic case the condition clinically mimicked ischaemic heart disease.

Case histories

Fig. 1 illustrates three generations of the family tree. All members of generations II and III, except one, II. 5, were examined, while electrocardiograms and information about other members were obtained indirectly where possible. None of the spouses of generation II suffered from heart disease or gave any history of familial heart disease.

Case II. 1 A 37-year-old housewife complained of palpitations and of recurrent praecordial pain radiating into both arms as far as the hands, during her first pregnancy at age 22. The chest pain and attacks of rapid palpitations recurred at age 32 and continued. The chest pain was symmetrical and occurred upon moderate exertion, excitement, and frequently soon after retiring to bed at night. It was relieved by nitroglycerin, and at night by sitting or standing up. A course of propranolol completely relieved her chest pain.

Her signs included a prominent jugular venous 'a' wave, a mild left parasternal impulse, and a loud ejection murmur at the left sternal edge in the third left interspace (Fig. 2). The second heart sound was widely split and the pulmonary component was accentuated. The murmur was abolished during the straining phase of the Valsalva manoeuvre. The 'a' wave ratio of the apex cardiogram was 15 per cent (Benchimol and Dimond, 1962). The chest films showed no cardiac enlargement but the main pulmonary arterial segment was prominent (Fig. 3). A systolic pressure gradient of 15 mm. Hg was found across the pulmonary infundibulum, but no gradient was seen in the left ventricle. Selective coronary arteriography was normal.

Case II. 2 The dizygotic twin sister of Case II. 1 complained of recurrent upper left praecordial pain and a sensation of swelling of the left arm, during her fourth pregnancy at age 31. The pain was precipitated by exertion or excitement, frequently occurred on retiring to bed at night, and was relieved by sitting up. She noticed that exertional pain was relieved by sitting but not by lying down. She denied central chest pain and radiation to the neck or right arm. Her arterial and venous pulse contours and cardiac impulses were normal clinically. An ejection murmur was heard at the left sternal edge and the second heart sound was widely split without appreciable respiratory variation. Her chest film showed prominence of the main pulmonary artery (Fig. 3). Cardiac catheterization including selective coronary arteriography showed no abnormalities.

Case II. 3 A 41-year-old farmer was noted to have an intermittent cardiac murmur, particularly after exercise, at age 22. He had fainted frequently in his youth, but otherwise had no symptoms until age 33, when praecordial chest pain and fatigue

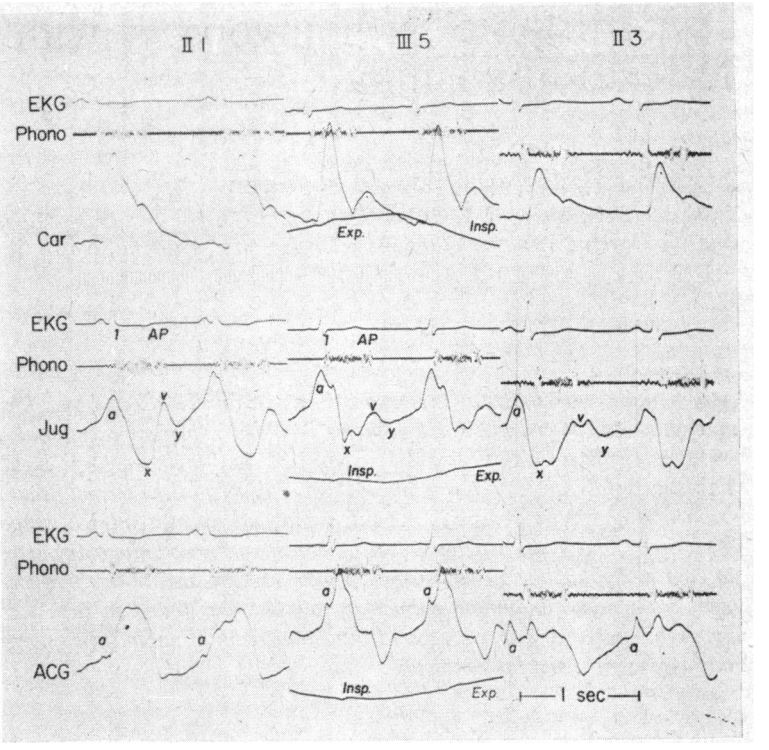


FIG. 2 *Phonocardiograms (Phono), external carotid arteriograms (Car.), external jugular phlebograms (Jug.), and apex cardiograms (ACG) from subjects III. 1, III. 5, and II. 3. The phonocardiograms are recorded with a crystal microphone[1] from the third left interspace at the left sternal edge. The pulses and apex impulses were recorded with a pulse wave crystal microphone.[2] The tracings were made with an optical recorder[3] at a paper speed of 100 mm./sec. The gradations between the upper and middle row of panels represent 40 msec. intervals.*

were precipitated by exertion or excitement. For several years he often obtained relief by squatting but little or no relief from nitroglycerin. The signs included a sustained apical impulse with a palpable presystolic component (Fig. 2), and an ejection murmur at the left sternal edge. The 'a' wave ratio of the apex cardiogram was 40 per cent. Chest films showed slight left ventricular enlargement and prominence of the main pulmonary arterial segment (Fig. 3). A right ventriculogram showed heavy trabeculation and infundibular narrowing especially during systole (Fig. 4), associated with a pressure gradient of 23 mm. Hg. No

[1] Model SP-5S, Schure Brothers, Inc., Evanston, Illinois.
[2] Model S374, Sanborn Company, Cambridge, Massachusetts.
[3] Model DR-8, Electronics for Medicine, Inc., White Plains, N.Y.

gradient between the left ventricular inflow tract and the outflow tract or apex was found at rest, following extrasystoles or during infusion of isoprenaline. The left ventriculogram showed increased wall thickness. Selective coronary arteriograms were normal.

Case II. 4 A 39-year-old building contractor first noticed effort intolerance with breathlessness and central chest discomfort at age 30, but these did not progress. Attacks of rapid palpitations began at the age of 37.

Clinically there was a prominent jugular venous 'a' wave, but the apex impulse was normal. There were no cardiac murmurs at rest. The second heart sound was widely split and fixed with respect to respiration. The average 'a' wave ratio of the apex cardiogram was 24 per cent. Inhalation of isoprenaline produced a loud late systolic ejection murmur at the left sternal edge (Fig. 5), and accentuated the jugular venous 'a' wave. Chest films showed slight prominence of the main pulmonary arterial segment and slight left ventricular enlargement (Fig. 3).

Case II. 5 The eldest sib of generation II suffered from recurrent attacks of prolonged left anterior chest pain associated with numbness in both hands and arms from the age of 31. No cardiac murmurs were noted. The electrocardiogram disclosed a normal PR interval, an abnormal P terminal force (Morris *et al.*, 1964), and symmetrical T wave inversion in leads V4–6. At age 41 he suffered a fatal car accident, the cause of which was not apparent. He was driving alone and may have died suddenly at the wheel. A necropsy was not performed.

Case III. 2 Age 16, the eldest son of II. 3, was asymptomatic. His arterial and jugular venous pulse contours were normal. The apex impulse was mildly sustained. There was a short midsystolic murmur accentuated by the inhalation of isoprenaline. The second heart sound was normal. The PR interval was short (Fig. 6). The total amplitude of lead V2 exceeded 65 mm. The ST segment in lead V6 was horizontally depressed by between 0·5 and 1·0 mm.

Case III. 5 At age 15, the eldest son of II. 1 was asymptomatic. His arterial pulse was normal but there was a prominent jugular venous 'a' wave and a left parasternal impulse. A midsystolic murmur was heard at the left sternal edge. The second heart sound was widely split but narrowed during expiration. The apex cardiogram showed an 'a' wave ratio of 27 per cent (Fig. 2).

Case III. 10 Age 17, the eldest son of II. 2 was asymptomatic. His apical impulse was slightly sustained, and a presystolic component could be easily felt. There was a midsystolic murmur at the left sternal edge. Inhalation of isoprenaline accentuated the murmur and increased the average 'a' wave ratio of the apex cardiogram from 25 to 54 per cent. The electrocardiogram (Fig. 6) showed greatly increased QRS amplitude in the chest leads. The J point was depressed in the lateral chest leads with an upward sloping ST segment.

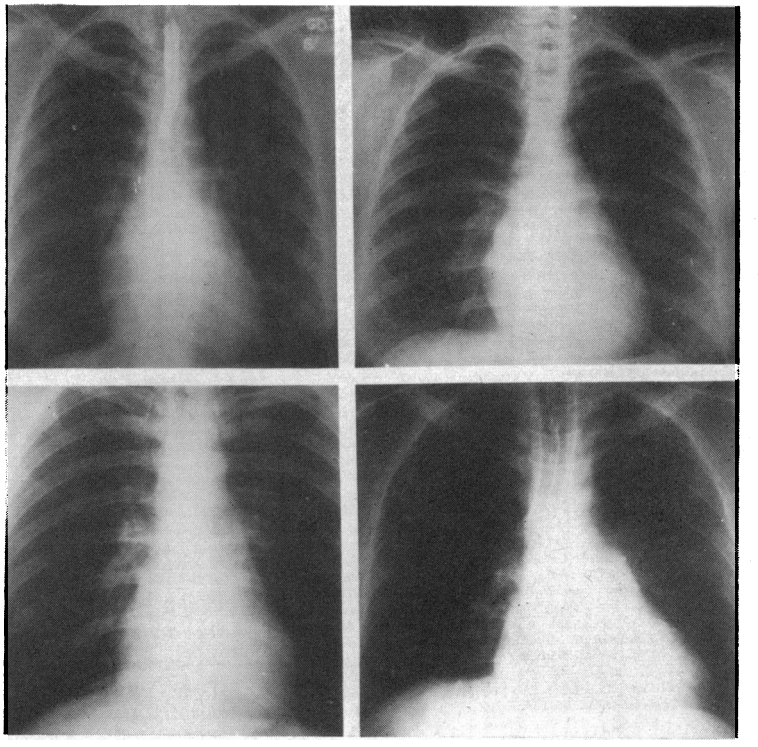


FIG. 3 *Postero-anterior chest films of II. 1* (upper left), *II. 2* (upper right), *II. 3* (lower left), *and II. 4* (lower right). *Note the mild prominence of the main pulmonary arterial segment.*

Other members of the family In generation I several members of the paternal side of the family were thought to have heart disease. I. 4 has suffered from recurrent exertional chest pain for four years. His electrocardiogram showed an abnormal P terminal force, a PR interval of 0·17 sec., and small Q waves in leads I, II, and V4–6 but no increase in QRS amplitude and no ST-T abnormalities. I. 2 has had a number of attacks of prolonged severe chest pain but without change in the electrocardiogram or the serum enzymes. He had no cardiac murmurs. His electrocardiogram displayed an abnormal P terminal force, a PR interval of 0·18 sec., and right bundle-branch block but no increased QRS amplitude or ST-T abnormalities. I. 1 suffered from recurrent attacks of tachycardia and her activity was limited.

Discussion

At least 7 members of this family appear to be affected by a form of hypertrophic cardiomyopathy. The fully developed condition is characterized clinically by recurrent exertional

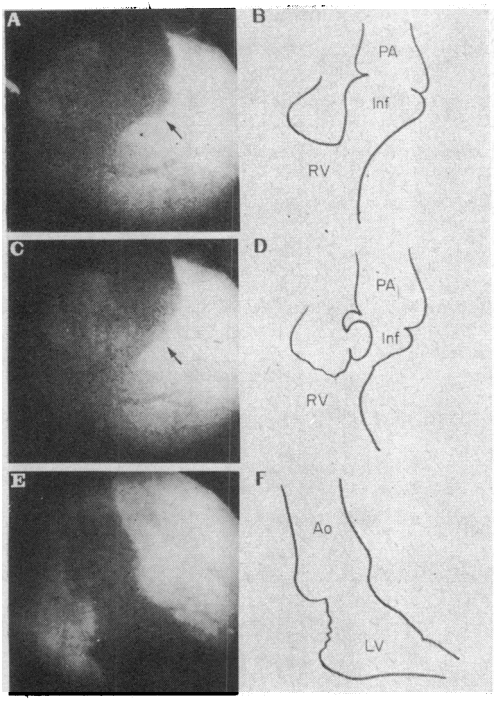


FIG. 4 *Single 16 mm. frames from cine-angiograms in patient II. 3. A and B show right ventricular outflow tract at the end of diastole in the antero-posterior position. C and D show the same at the end of systole. Note the hypertrophied masses of myocardium and the infundibular chamber (Inf). E and F show the left ventricular outflow tract at the end of systole in the right anterior oblique position. There is no sign of outflow obstruction.*

and recumbent praecordial pain associated with discomfort in the hands, and bouts of rapid palpitations. The signs include large apical and jugular venous 'a' waves, a left parasternal midsystolic murmur, and wide splitting of the second heart sound. The electrocardiogram typically displays a borderline short PR interval, increased QRS amplitude in the chest leads, and persistent ST depression. Radiologically there is little or no cardiomegaly, but prominence of the main pulmonary artery segment is present. The abnormality appears to be inherited through an autosomal Mendelian dominant gene with incomplete penetrance, though it is possible that the unaffected members of generation III will develop signs of the disorder as they grow older. There has been no consanguinity in the last two generations of this family. However, they form part of a group of families interrelated by marriage, who have lived in eastern North Carolina for several generations.

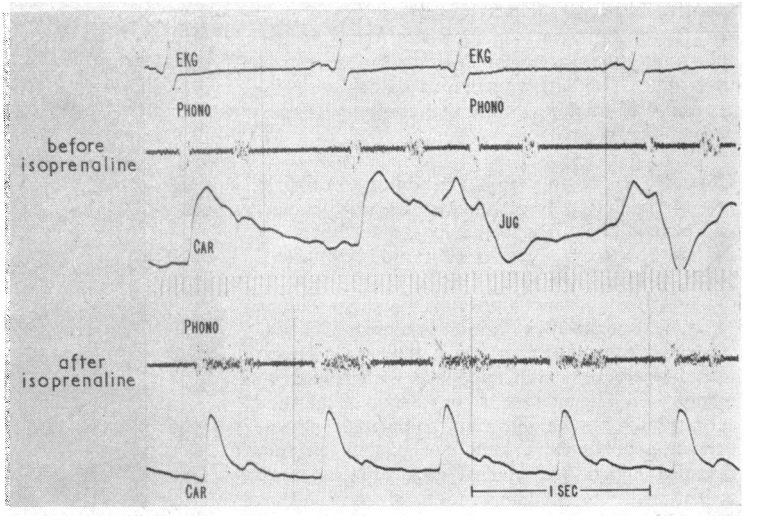


FIG. 5 *Phonocardiogram (Phono) with external carotid arteriogram (Car) and external jugular phlebogram (Jug) before inhalation of isoprenaline, and phonocardiogram with external carotid arteriogram after isoprenaline in II. 4. Note the appearance of a systolic murmur and the change in contour of the carotid pulse after isoprenaline.*

FIG. 6 *Electrocardiograms from subjects III. 2* (top), *III. 5* (middle), *and III. 10* (bottom). *Where indicated the tracings are half standard* ($\times 1/2$).

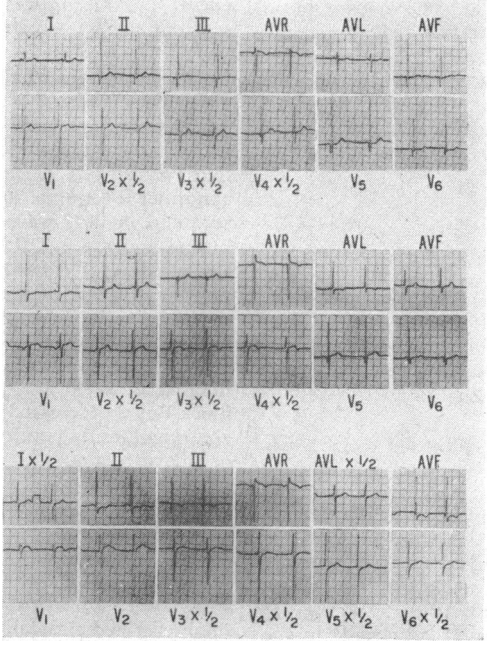


TABLE 1 *Clinical findings*

Patient	*Symptoms*			*Physical signs*				
	Recurrent chest pain	*Recurrent palpitations*	*Hand swelling*	*Large jugular venous 'a' wave*	*Presystolic apical impulse*	*Sustained apical impulse*	*Left parasternal impulse*	*Systolic murmur*
II. 1	+	+	−	+	−	−	+	+
II. 2	+	−	+	−	−	−	−	+
II. 3	+	+	+	−	+	+	+	+
II. 4	+	+	+	−	+	+	+	+
II. 5	+	−	−	...	...	...	...	−
III. 2	−	−	−	−	−	+	−	+
III. 5	−	−	−	+	−	−	+	+
III. 10	−	−	−	−	+	+	−	+

Symptoms All members of generation II of the family presented with chest pain, though this was the presenting symptom in only 10 per cent of a series of patients with hypertrophic subaortic stenosis described by Frank and Braunwald (1968). The chest pain affected the left praecordium in three members of generation II but was symmetrical and anterior in the fourth. It was often prolonged (Whitfield, 1961) and occurred on retiring to bed at night but before falling asleep in contrast to nocturnal angina (Smith and Papp, 1962). The sitting position afforded relief from both recumbent and external pain. Similar recumbent chest pain occurred in one member of a family with cardiomegaly described by Westlake, Cohen, and Willis (1962). II. 3 found that he was able to obtain relief from pain by squatting. Nellen and associates (1967) noted that this manoeuvre either diminished or abolished the systolic murmur in hypertrophic obstructive cardiomyopathy.

II. 2, II. 3, and II. 4 complained of subjective swelling of the left arm and hand, reminiscent of the shoulder-hand syndrome after myocardial infarction (Edeiken, 1957).

Physical signs Prominent jugular venous 'a' waves and large 'a' waves in the apex cardiogram both occur in hypertrophic cardiomyopathy (Braunwald *et al.*, 1964; Wigle, Heimbecker, and Gunton, 1962; Horlick *et al.*, 1966). The presence of large jugular venous 'a' waves and the situation of the murmur suggested right ventricular involvement, and this appeared to be the case in 2 of the 3 patients who were catheterized.

In 4 patients the second heart sound was widely split and the degree of splitting varied only slightly with respiration (Table II, columns 7 and 8). Phonocardiograms showed that, in each case, the pulmonary component followed the aortic component. Paradoxical splitting of the second heart sound and a single second heart sound were observed in a number of the patients described by Frank and Braunwald (1968). Haemodynamic evidence of obstruction to right ventricular outflow was present in 15 per cent of their patients, but abnormally wide splitting of the second heart sound was not observed. Pulmonary closure was delayed in a patient with narrowing of the infundibulum of the right ventricle and a very thick left ventricular myo-

TABLE 2 *Electrocardiographic and phonocardiographic findings*

Patient	*PR interval (sec.)*	*QRS axis (°)*	*R/S in V1 (mm.)*	*R/S in V5 (mm.)*	*ST segment in V5 (mm.)*	*P terminal force < −0·04*	*Interval between components of second heart sound (msec.)*		*Resting heart rate (beats/min.)*	*Carotid pulse*	
							Insp.	*Exp.*		*Upstroke time (msec.)*	*Ejection time (msec.)*
II. 1	0·12	+40°	11/5	16/0	−2·0	−	80	65	67	80	290
II. 2	0·13	+40°	5/23	38/0	−3·0	+	60	50	60	120	300
II. 3	0·17	+30°	3/19	27/7	−1·0	+	30	10	57	100	305
II. 4	0·12	−20°	3/19	28/20	−1·5	+	65	60	65	60	285
II. 5	0·16	+ 5°	1/9	7/3	0	+	...	...	...	...	...
III. 2	0·11	+80°	12/24	26/6	−0·5	−	...	...	...	...	...
III. 5	0·11	0°	8/25	27/15	+0·5	+	60	45	63	105	295
III. 10	0·14	+85°	3/20	44/54	J −	−	20	10	65	125	290

cardium described by Goodwin and associates (1961). The second sound was, however, noted to be normal in a similar case described in the same report. Three patients with right ventricular involvement from a completely affected sibship of five in the family described by Hollman and associates (1960) had widely split second heart sounds. In hypertrophic subaortic stenosis, delay of the aortic component of the second heart sound has been related to the severity of the obstruction (Frank and Braunwald, 1968). It might seem that the pulmonary component is delayed in patients with right ventricular obstruction for the same reason. None of the present series, however, had evidence of severe obstruction. Two patients described by Bishop and associates (1962) had well-marked splitting of the second sound but no evidence of right ventricular obstruction was noted, in one case by catheterization and in the other at necropsy. Karatzas, Hamill, and Sleight (1968) also describe 3 patients without obstruction in whom there was wide splitting of the second sound and little or no respiratory variation. It seems possible therefore that delay of the pulmonary component may be due to conduction delay resulting from this type of hypertrophy.

Electrocardiogram The normal QRS duration excludes typical pre-excitation though it is now well known that this has a familial incidence (Harnischfeger, 1959) and has been described in association with hypertrophic subaortic stenosis (Frank and Braunwald, 1968) and familial cardiomegaly (Westlake *et al.*, 1962). Initial slurring of the QRS complex with a short PR interval has been attributed to increased activation time in the grossly hypertrophied septum (Coyne, 1968). Though four members of the family described by Westlake and associates (1962) had the classic Wolff-Parkinson-White syndrome, six others showed a borderline pre-excitation syndrome. The presence of both typical and borderline examples of pre-excitation in the same family suggests that both are manifestations of the same abnormality. Though no tachyarrhythmias have been documented in the present series, three members of generation II suffered from bouts of rapid palpitations.

The degree and pattern of the persistent ST depression in the present series resembles that documented by Westlake and associates (1962) and Karatzas and associates (1968). Attention has been drawn to the combination of inverted T waves, ST depression, a short PR interval, and paroxysmal tachycardia in several families by Hilmer (1966). These observations support the concept that an abnormality of conduction may form an intrinsic part of hypertrophic obstructive cardiomyopathy.

Haemodynamic findings Right-sided gradients are common in hypertrophic subaortic stenosis (Frank and Braunwald, 1968), but isolated right-sided muscular infundibular stenosis in adults seems to be uncommon (Goodwin *et al.*, 1961; Taylor, Bernstein, and Jose, 1964). Five non-familial cases have been reported by Grosse-Brockhoff and Loogen (1962).

The first three patients in generation II were initially thought to have ischaemic heart disease and underwent coronary arteriography, but no localized abnormalities were found. The widespread use of coronary arteriography has brought to light an increasing number of patients thought to have ischaemic heart disease in whom no coronary artery disease can be seen angiographically (Kemp, Elliott, and Gorlin, 1967). Since the present series of patients mimicked ischaemic heart disease rather closely, hypertrophic cardiomyopathy should be considered as a possible explanation of apparent ischaemic heart disease without coronary arterial disease even when intraventricular pressure gradients cannot be shown.

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