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Analysis of symptomatic course and prognosis and treatment of hypertrophic obstructive cardiomyopathy

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The symptomatic history of 85 patients with hypertrophic obstructive cardiomyopathy is presented and, where appropriate, correlated with the clinical data, electrocardiography, radiography, angiocardiography, and haemodynamic results. The effects of pregnancy on the disorder and the occurrence of infective endocarditis are discussed.

Young age at detection, absence of left atrial hypertrophy on the electrocardiogram, and a relatively low left ventricular end-diastolic pressure are favourable features which may be associated with many more asymptomatic years. Some children may, however, have the disease in severe form and sudden death can occur at any age. It may be more common in familial patients. A significantly raised end-diastolic pressure in the left ventricle may provide the closest correlation with the risk of sudden death which is likely to be due to high inflow resistance and tachycardia or to loss of atrial drive.

Patients who present asymptomatically, or with minor symptoms, tend to run a more favourable course than those with severe symptoms. Proven familial cases do not appear to be more severe. They were less common in this study than in many other studies, but because of the rigid criteria imposed for inclusion in the familial group, many familial patients may have been included in the sporadic group. Deterioration was associated with clinical and haemodynamic signs of left ventricular inflow resistance. Atrial fibrillation is rare, but is poorly tolerated, and is a serious complication.

Longer term studies of the effects of medical and surgical treatment are necessary before a full appraisal of these forms of therapy can be made.

Hypertrophic obstructive cardiomyopathy is a disease of relatively recent recognition which is known in North America as idiopathic hypertrophic subaortic stenosis The details of the disease have been reported previously (Braunwald *et al.*, 1960, 1964; Goodwin *et al.*, 1960; Wigle, Heimbecker, and Gunton, 1962; Goodwin, 1967; Cohen *et al.*, 1964).

It is the purpose of this paper to report our experience of the long-term follow-up of patients with hypertrophic obstructive cardiomyopathy with reference to symptoms and the occurrence of sudden death, and with comments on treatment. We have attempted to relate the symptoms and signs of the patients, together with their more objective features, when initially seen, to the subsequent course of the disease.

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The patients (*Table 1*)

This study covers 85 patients with hypertrophic obstructive cardiomyopathy who have been followed at Hammersmith Hospital for up to 10 years. All patients included in this study have been seen at least twice and, if living, have been seen during the previous year. Seventy patients (82%) were sporadic and 15 (18%) were proven to be on a familial basis. It is likely that the familial incidence is really higher than this, for we have only included under this heading patients in whom a relative had been proven to have the disease. The diagnosis was made on solely clinical grounds without haemodynamic or angiographic studies in only 5 patients (6%). In all 5, the combination of a proven family history, typical physical signs,

TABLE 1 *General features of 85 patients with hypertrophic obstructive cardiomyopathy*

Sporadic: familial	70:15
Male:female	45:40
Youngest	2·5 yr
Oldest	55 yr
Asymptomatic	27 patients (27%)
Mean follow-up	4·0 yr
Total follow-up	360·2 patient years
Follow-up 5 yr	21 (25%)
Follow-up 2 yr	15 (18%)
Longest follow-up	12 yr
Duration of symptoms when first seen	
Average	8·1 yr
0–5 yr	45 (53%)
6–10 yr	22 (26%)
11–15 yr	13 (15%)
16–20 yr	5 (6%)
Basis of diagnosis	
Clinical	5 (6%)
Angiographic	10 (12%)
Haemodynamic	70 (82%)

TABLE 2 *Presentation according to class and subsequent fate*

Class I			
Average age onset	13·9		
Average age included	21·6	23 Cases	21 Same: 16 Sporadic, 5 Familial
			2 Sudden death. Sporadic
Class II			
Average age onset	27·6		
Average age included	35·8	51 Cases	17 Same: 15 Sporadic, 2 Familial
			16 Better: 15 Sporadic, 1 Familial
			9 Deteriorated: 7 Sporadic, 2 Familial
			9 Dead: 6 Surgical: 5 Sporadic, 1 Familial; 3 Sudden: 2 Sporadic, 1 Familial
Class III			
Average age onset	24·9		
Average age included	29·3	10 Cases	1 Same. Sporadic
			5 Better: 3 Sporadic, 2 Familial
			3 Deteriorated. Sporadic
			1 Sudden death. Sporadic
Class IV		1 Case	Better Familial
Age, onset	31		
Age, included	34		

and characteristic phonocardiographic responses to pharmacological stimulation (Goodwin *et al.*, 1964) made the diagnosis certain. In all other cases the diagnosis was confirmed by haemodynamic and angiocardiographic studies (Cohen *et al.*, 1964; Simon, Ross, and Gault, 1967). In 10 patients (12%) there was neither a resting gradient across the outflow tract of the left ventricle nor a gradient after provocation, but in these the combination of the clinical picture and unmistakable angiographic appearances also made the diagnosis certain. The remaining 70 patients had typical haemodynamic and angiographic abnormalities. Further confirmation was obtained in those who came to operation or necropsy.

Forty-five (52%) were male and 40 (48%) were female. The youngest included in the series was 2½ years old; the oldest was 55 years at the time of inclusion. The longest follow-up was 12 years, the shortest 6 months. Twenty-one patients (25%) were followed for more than 5 years, 15 (18%) for less than 2 years. The average follow-up was 4·0 years. Twenty-three patients (27%) were asymptomatic on ordinary activity when first seen. Forty-five patients (53%) had had symptoms for less than 5 years when first seen, 22 (26%) from 6 to 10 years, and 13 (15%) from 11 to 15 years. Only 5 had had cardiac symptoms for more than 15 years when first seen. The average duration of symptoms or of recognition of a murmur without symptoms was 8·1 years.

There were 12 deaths (14%), 6 postoperative, 6 sudden; 2 died from infective endocarditis (one due to a ruptured cerebral mycotic aneurysm), and one was due to an unrelated neurological condition.

Presentation and progress according to symptoms (*Table 2*)

The symptoms have been graded according to the New York Heart Association functional classification (1964). *Class I:* no disability on ordinary activity. *Class II:* slight limitation of physical activity by symptoms. *Class III:* obvious limitations by symptoms. *Class IV:* inability to perform any physical activity without symptoms.

Twenty-three patients (27%) were in Class I when seen initially. Of these, 5 were familial and 18 sporadic. Two of the sporadic patients have died suddenly; the remaining 21 patients have stayed unchanged during the follow-up period. The average age at diagnosis in this group was 13·9 years, and the average age at inclusion into the series was 21·6 years, making an almost 8-year average interval between the initial detection of a murmur and referral, during which time no symptoms developed. The mode of discovery was either fortuitous detection of a murmur or examination because of a family history suggestive of heart disease.

Fifty-one of the 85 patients (60%) presented with Class II symptoms. Seventeen (33%) remained the same, 16 (31%) improved, and 9 (18%) deteriorated during the course of follow-up. Nine patients died, 6 after surgical treatment, 2 suddenly and unexpectedly, and 1 from infective endocarditis. Both the average age of detection (27·6 years) and of inclusion into the series (35·8 years) was higher than in the preceding group.

Ten patients (11%) presented with Class III symptoms. Five (50%) improved, 3 (30%) deteriorated, 1 (10%) remained the same, and 1 (10%) died. The average age of onset in these was 25·9 years, which is similar to those with Class II symptoms. However, the average age at inclusion into the series (29·3 years) was less than in Class II, perhaps indicating a more rapidly progressive form of the disease in this group.

One patient, aged 34, presented initially in

Class IV status. Since stopping digitalis and nitroglycerin which he had been taking, and since the institution of propranolol, he has reported symptomatic improvement. He is now, approximately 8 months later, in Class III status. He presented with a clinical picture very suggestive of ischaemic heart disease, with pathological Q waves in the praecordial leads of the electrocardiogram, congestive heart failure, and a mitral systolic murmur thought to be due to papillary muscle dysfunction. Subsequent haemodynamic and angiographic data confirmed the diagnosis of hypertrophic obstructive cardiomyopathy. Coronary arteriography was normal (Fig. 1).

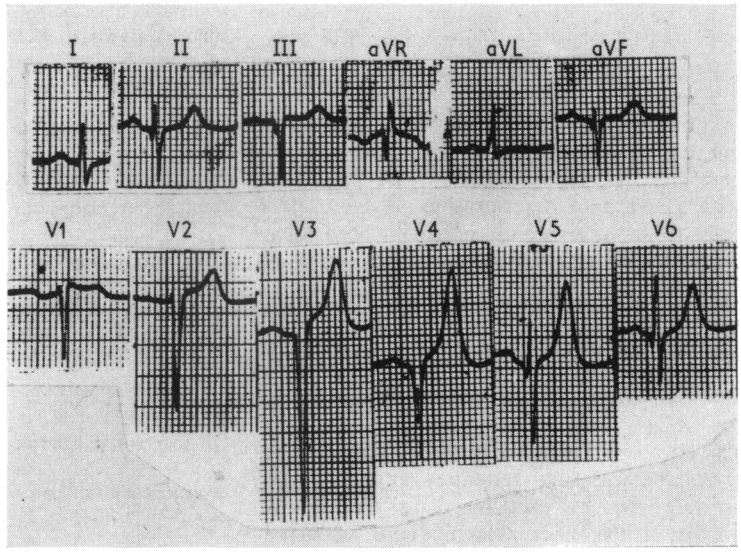


FIG. 1 *Pseudo-infarction electrocardiogram of a patient who presented with Class IV symptoms and was initially diagnosed as ischaemic heart disease. It demonstrates changes consistent with a diaphragmatic and anterior wall myocardial infarction. The record had been normal 14 years earlier in 1954.*

Analysis of fate of patients

We have attempted to analyse the symptomatic course of each patient in relation to the condition at the time of the most recent examination compared with the first consultation. Frank and Braunwald (1968) have noted the fluctuating course of the symptoms and signs in many but not all patients, and our experience agrees with this. Eliminating the 6 patients who died suddenly and the 6 who died after operation, there are 73 patients remaining: first, those who have remained stable (group A); second, those who have improved by at least one symptomatic class (group B); and third, those who have deteriorated (group C). Group C includes 2 patients who died – one of infective endocarditis, who before the onset of infection had pursued a downhill course; the other of an acute inflammatory neurological lesion, whose cardiac status had been steadily worsening before that.

Clinical features (*Table 3*)

Symptoms (group A) There were 39 patients, 32 of whom were sporadic and 7 familial. The average age at onset of symptoms was 20·3 years and 23 (59%) were discovered before their 20th birthday. The average duration of symptoms when first seen was 8·3 years. Twenty-one (54%) were asymptomatic when first seen, 17 (44%) had Class II symptoms, and one had Class III symptoms.

Symptoms (group B) There were 22 patients, 18 sporadic and 4 familial. The average age at onset was 25 years and the average duration of symptoms when first seen was 5·7 years. These patients were significantly older (P = <0·01) at onset than those in group A. Sixteen (74%) presented with Class II symptoms, 5 (23%) with Class III symptoms, and one with Class IV symptoms. The severity of symptoms was unrelated to the sex of the patient. The discovery of a murmur or initial symptoms had been noted in 10 (46%) before their 20th birthday, a lower percentage than in the preceding group. The average duration when first seen was 5·7 years.

Symptoms (group C) There were 12 patients, the average age at onset being 30·0 years, greater than either group A or B. The mean duration of symptoms when first seen was 6·9 years. Nine (75%) originally presented with Class II symptoms and 3 (25%) with Class IV symptoms.

TABLE 3 *Clinical summary of groups A, B, and C – 73 patients, 60 sporadic, 13 familial*

	Group *A – Stable*	*B – improving*	*C – worse*
No. of patients	39	22	12
Age onset (yr)	20·3	24·5	30
Age presenting (yr)	28·6	31·2	36·9
Duration of symptoms (yr)	8·3	5·7	6·9
No. of patients with onset <20 yr	23 (59%)	10 (45%)	4 (38%)
Class I	21 (54%)	—	—
Class II	17 (44%)	16 (74%)	9 (75%)
Class III	1 (2%)	5 (23%)	3 (25%)
Class IV	—	1 (4%)	—

All patients who showed symptomatic deterioration had symptoms when first seen. Of those patients who remained stable, the majority (59%) were under 20 years when the first evidence of disease appeared, harmonizing with Frank and Braunwald's (1968) experience that early onset tends to be associated with absence of deterioration. But our data refer to symptoms and, as will be seen later, early onset and static course do not protect against sudden death.

Dyspnoea was the most common initial symptom, occurring with approximately equal frequency among the symptomatic patients in all three groups. At the time of inclusion in the series, almost all symptomatic patients also had additional symptoms which were, in order of decreasing frequency, angina, palpitations, syncope, oedema, and paroxysmal nocturnal dyspnoea. Haemoptysis occurred in one patient. Peripheral oedema was rare, occurring only in the one Class IV patient, and in 3 women during pregnancy, when the oedema was not thought to be of cardiac origin. Moderate ankle oedema, orthopnoea, and pulmonary congestion occurred in the third trimester of pregnancy in one patient.

There seemed to be no characteristic pattern of symptoms that were associated with progression of the disease.

Physical signs The usual signs of hypertrophic obstructive cardiomyopathy were present to some degree in all our patients when first seen. A late ejection systolic murmur ascribed to left ventricular outflow obstruction and mitral regurgitation was invariably present, usually Grade 3 to Grade 4 in intensity. Clinical evidence suggesting diminished ventricular compliance, as judged by a palpable left atrial presystolic beat and diminishing systolic murmur, was more common in patients in group C than in either group A or B. A rise in the jugular venous pressure was frequent in all 12 patients and a prominent right atrial sound was associated with an augmented 'a' wave in 11 (93%). We feel that these are important physical signs which are a clue to the loss of ventricular compliance which occurs in these patients.

Subsequent study has revealed a characteristic pattern of deterioration in which the rise in left atrial pressure may be followed by atrial fibrillation and embolism (Oakley, 1971a).

Radiography The chest radiographs were more often normal in group A (51%) than in group B (14%) or group C (8%), but there was no difference between the latter two groups. The most common abnormality was left ventricular enlargement. Left atrial enlargement was more common in group B (85%) and C (93%) than in group A (49%).

Serial chest films showed increasing heart size in 4 (10·3%) patients in group A, in 1 (4·5%) patient in group B, and in all patients in group C. Increasing cardiac size thus accompanied symptomatic deterioration (Fig. 2).

Electrocardiography (Table 4) There were 3 totally normal electrocardiograms in the series, all 3 being found in asymptomatic patients: these have remained normal throughout follow-up.

Frontal plane axis

In 59 (82%) of the 73 patients the mean frontal QRS vector fell between 0° and +90°. A normal frontal QRS axis occurred more commonly in group A (88%) than in either group B (68%) or group C (75%).

Axis deviation

Left axis deviation (0° to −90°) occurred in 4 (10%) patients in group A, 6 patients (27%) in group B, and 1 patient (8%) in group C. Right axis deviation (> +90°) occurred in 1 patient in groups A and B and in 2 patients in group C.

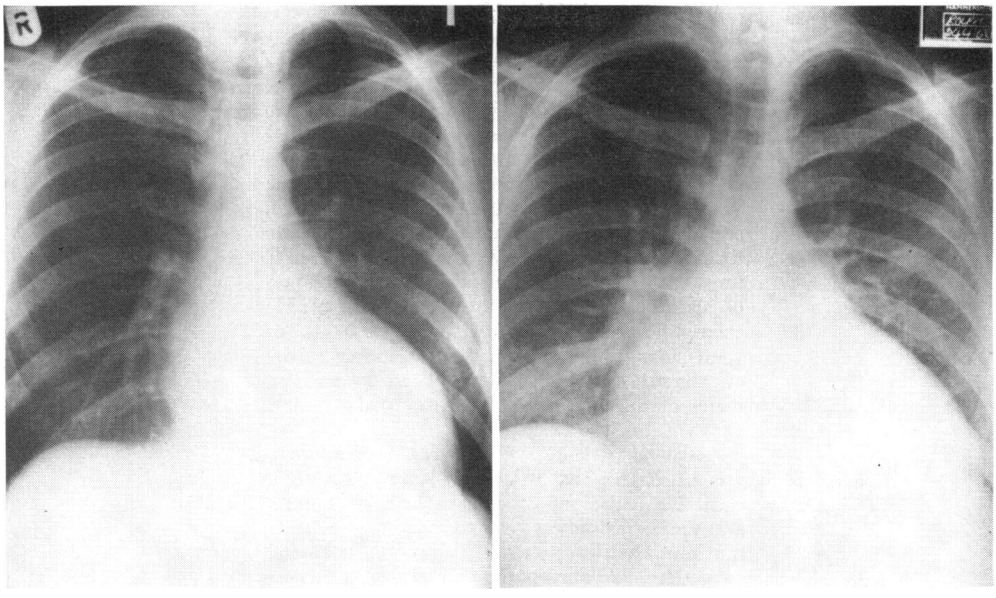
Atrial enlargement

Electrocardiographic evidence of left atrial hypertrophy, consisting of a 'P' wave duration in lead II of greater than 0·10 mm, occurred significantly less often in group A (20%) than in either group B (50%) or group C (42%). The difference between groups B and C is not significant. Right atrial hypertrophy (a 'P' wave amplitude in lead II greater than 2·5 mm) was present in 2 patients. In both, a right ventricular outflow tract gradient was present.

Electrocardiographic evidence of left atrial hypertrophy was correlated positively with the average left ventricular end-diastolic pressure. Patients with left atrial hypertrophy had a mean LV end-diastolic pressure of 19±5 mmHg, but in those without left atrial hypertrophy the average end-diastolic pressure was 13±4 mmHg ($P = < 0{\cdot}01$).

Ventricular hypertrophy

The criteria used for the electrocardiographic diagnosis of left ventricular hypertrophy were as follows. $S_{V1} + R_{V5,6} = 35$ mv; RaVL = 11 mv; $R_I + S_{III} = 40$ mv (Sokolow and Lyon, 1949). In the series, 38 patients (52%) had one or more criteria for this diagnosis. Left ventricular hypertrophy occurred with similar frequency between the groups, and for this reason did not have a prognostic value. The electrocardiogram with the greatest voltage (Fig. 3) occurred in an asymptomatic boy, and 3 of our most seriously ill patients (at this point) have borderline low voltage. Patients having an electrocardiogram diagnostic of left ventricular hypertrophy had a mean peak resting left ventricular outflow gradient of 51



(a) (b)

FIG. 2a and 2b *Chest radiographs of a patient in 1958 (a) and 1968 (b) in group C. His clinical picture assumed congestive features, his murmurs became very faint, and he was subject to bouts of atrial fibrillation.*

mmHg. When left ventricular hypertrophy was absent the mean gradient was similar, being 49 mmHg. This is in contrast to Frank and Braunwald (1968) who found significantly higher gradients in those with left ventricular hypertrophy.

Intraventricular conduction

Spontaneous incomplete left bundle-branch block occurred in 4 patients (10%) in group A, 1 (4·5%) in group B, and 3 (25%) in group C. There were 8 patients with postoperative complete left bundle-branch block, 7 in group B and 1 in group C. Its presence postoperatively appeared to have no prognostic significance, while its production surgically is no longer felt to be necessary for relief of obstruction and symptomatic improvement (Bigelow *et al.*, 1966). Complete right bundle-branch block occurred in one patient in group B.

Q waves

Abnormally large Q waves, suggesting myocardial infarction, occurred in 9 patients (23%) in group A, in 3 patients (14%) in group B, and none in group C. This is a commonly recognized electrocardiographic occurrence in hypertrophic obstructive cardiomyopathy (Estes *et al.*, 1963; Prescott, Quinn, and Littmann, 1963), and is felt to be due to abnormal spatial orientation of the hypertrophied septum (Braudo, Wigle, and Keith, 1964), or to septal fibrosis (Wigle, 1964). Though many of our patients had a history of angina, in none of them was there a history of myocardial infarction, and we have found widely patent normal coronary arteries in 6 patients with hypertrophic obstructive cardiomyopathy who have undergone selective coronary arteriography.

Accelerated conduction

The established criteria for the diagnosis of the Wolff-Parkinson-White syndrome (Wolff, Parkinson, and White, 1930) is a PR interval of less than

TABLE 4 *Summary of electrocardiogram findings in groups A, B, and C*

	Group A	*Group B*	*Group C*
No. of patients	39	22	12
Normal electrocardiogram axis	3 (8%)	0	0
Normal	35 (88%)	15 (68%)	9 (75%)
Right	4 (10%)	6 (27%)	1 (8%)
Left	1 (3%)	1 (4%)	2 (17%)
Hypertrophy			
RA	0	1 (4%)	1 (8%)
LA	8 (20%)	11 (50%)	5 (47%)
RV	3 (8%)	1 (4%)	0
LV	18 (46%)	13 (59%)	7 (58%)
PR interval			
<0·13 sec	4 (10%)	0	2 (17%)
>0·21 sec	0	3 (14%)	1 (8%)
QRS complex			
ILBBB	4 (10%)	3 (14%)	4 (33%)
LBBB	0	7* (32%)	1* (8%)
RBBB	0	1 (4%)	0
'Pseudoinfarct' pattern	9 (23%)	3 (14%)	0

* Postoperative.

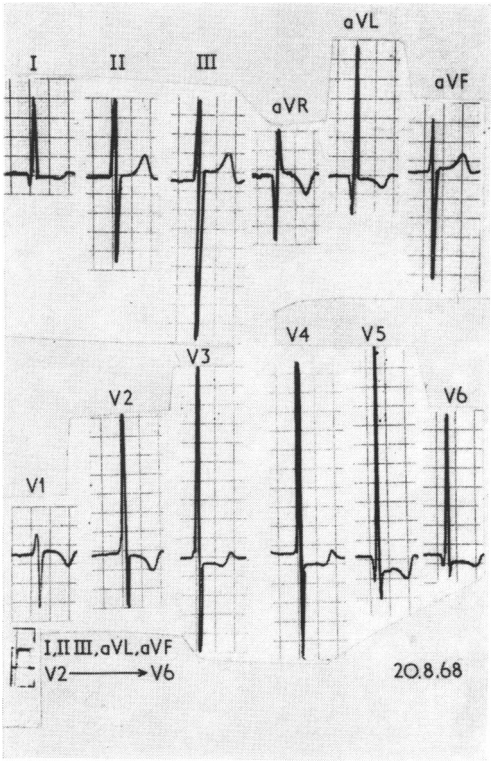


FIG. 3 *Electrocardiogram taken in 1968 of a 16-year-old boy who has been followed for approximately 8 years. The electrocardiogram, which was almost identical in 1960, shows remarkable voltage, though the patient is only mildly symptomatic.*

0·13 msec, the presence of a delta wave, and prolongation of the QRS complex. Though their criteria were not met in any of our patients, an abnormally short PR interval occurred in 4 patients in group A and 2 in group C. Two of these had delta waves, but none had QRS prolongation. None experienced supraventricular tachycardia, and none was familial.

Though serial graphs were available for review in many patients, we witnessed few significant changes in any during the course of follow-up, though subsequent analysis revealed the development of left axis deviation, Q waves, or widening of the QRS in 6 patients (Oakley, 1971a; Goodwin, 1970).

Atrial fibrillation

Atrial fibrillation is uncommon in hypertrophic obstructive cardiomyopathy. In Frank and Braunwald's (1968) large series, it occurred in 8 per cent. In our series we have observed it in 4 (4·7%) patients, 3 men aged 17, 33, and 37 and one woman of 49. In 3, atrial fibrillation was paroxysmal, and in one it was established; the latter died suddenly.

The youngest of these patients, a boy who was diagnosed at the age of 12 years, had his only known episode of arrhythmia at the age of 14 years. This caused a considerable worsening of his symptoms and the development of congestive heart failure. When in sinus rhythm, his cardiogram showed obvious biatrial hypertrophy and complete left bundle-branch block. Over the years, the signs of obstruction have diminished, and the difficulty now appears to be a greatly heightened resistance to ventricular inflow. He is unusual because of the severity and progression of his illness in relation to his age (Fig. 4). He exemplifies the tendency to progressive loss of ventricular outflow obstruction as inflow resistance increases, which has now been observed in many of our patients (Goodwin, 1970; Oakley, 1971b).

A second patient, a 33-year-old Maltese man, was in established atrial fibrillation when first seen. He had signs of congestive heart failure, and there was only a very unimpressive ejection murmur. He was erroneously diagnosed as having congestive cardiomyopathy and treated conservatively with digitalis and diuretics. He died suddenly, and a necropsy showed the typical features of hypertrophic obstructive cardiomyopathy.

A third man mirrors the clinical picture of the first patient. At a later age, he has shown progression of congestive signs and symptoms. The outflow murmur which was reported as grade III 5 years ago is now grade I in intensity. A recent episode of paroxysmal fibrillation caused an added degree of congestive cardiac failure, and frank pulmonary oedema was seen on the chest radiograph. Though cardioversion to sinus rhythm relieved some of his symptoms, there has been a steady deterioration over the years.

The fourth patient, a 49-year-old woman, presented a somewhat more encouraging picture. She was followed at Hammersmith Hospital for 6 years, though a cardiac murmur was first heard at the age of 18 years. During the course of follow-up she remained in Class II. More recently she was treated with propranolol. She had several episodes of fibrillation during which she deteriorated to Class III. However, on reversion to sinus rhythm, she returned to her usual status. In contrast to the three men, the signs of outflow obstruction continued to dominate her clinical picture. Her electrocardiogram showed only borderline left atrial hypertrophy when in sinus rhythm.

Nevertheless, atrial fibrillation is usually a sinister manifestation of increasing resistance to ventricular filling and an indicator of an advanced stage of the disease. Subsequent experience revealed atrial fibrillation in 14 patients, all of whom deteriorated as a result of the loss of atrial 'drive' (Goodwin, 1970; Oakley, 1971a).

Haemodynamic data (*Table 5*)

Left ventricular outflow tract obstruction

The assessments of left ventricular gradients were available in 33 patients in group A, 22 patients in group B, and 9 in group C (Table 5). For uniformity, we have chosen the highest recorded

basal gradient in each patient. The average gradient was 41 ± 37 mmHg for all patients (Fig. 5).

In *group A* the average gradient was 36 ± 31 mmHg, 8 patients having no resting gradient. Four of these developed gradients after provocation with isoprenaline, one developed a postectopic gradient consistently, and an additional patient developed a gradient of 75 mmHg after exercise. The remaining 2 were not subjected to provocative drugs or manoeuvres.

The average gradient in *group B* was 70 ± 38 mmHg, being significantly greater than group A ($P = 0.001$). There were 2 patients without gradients at rest. There was no difference between the patients in Classes II or III in this group. One patient developed a gradient of 65 mmHg with isoprenaline, and the other was not tested in this way. The lone patient in Class II had a gradient of 100 mmHg.

The average gradient in the 9 patients in *group C* was 43 ± 35 mmHg, which is not significantly higher than group A, but less than group B ($P = 0.08$). In 3 patients (all initially with Class II symptoms) there was no resting gradient. Two of these developed gradients of 40 and 60 mmHg, respectively after provocation. The third patient developed no gradient despite provocation. She was the mother of three children who were proved to have the disease and of 2 more who are highly suspect. She had typical angiographic appearances of cardiomyopathy. These 3 patients all had a left ventricular end-diastolic pressure of 25–30 mmHg without an outflow gradient, indicating a high degree of resistance to *inflow* into the left ventricle.

Left ventricular end-diastolic pressure Left ventricular end-diastolic pressure measurements were available in 29 patients in group A, 20 in group B, and 9 in group C (Fig. 6). The average resting pressure was considerably less in group A (15·9 ± 6 mmHg) than in either group B (20·4 ± 8 mmHg) or in Group C (22·6 ± 8 mmHg). As could be predicted, it also bore some relation to symptom class. The average pressure for Class I patients was 14·6 ± 6 mmHg; for those with Class II symptoms, 17·5 ± 7 mmHg; and with Class III symptoms 27·1 ± 6 mmHg. It was significantly higher in those patients with Class III disability ($P = 0.004$), but no significant difference occurred between Class I and Class II patients. It has been our repeated clinical observation, as previously stated, that in patients whose symptoms are increasing, clinical evidence of a raised pressure becomes more prominent throughout the course of the disease.

Right ventricular outflow tract gradient The presence of a right ventricular gradient greater than 10 mmHg was found in 18 (38%) of 48 patients. There was no difference between the three groups A, B, or C. The average gradient for each group was 29·6, 26·5, and 25 mmHg, respectively. The presence of a right ventricular gradient did not appear to have important clinical significance. The gradients were always lower than the left ventricular gradient in the same patients and

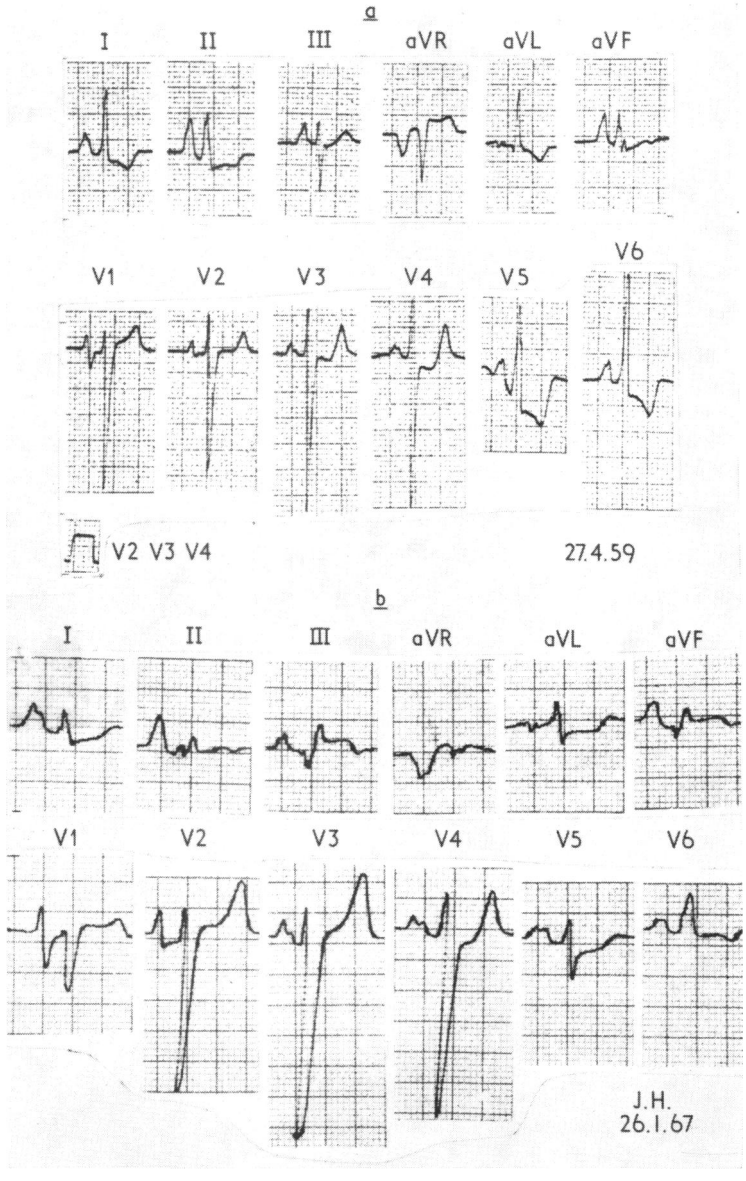


FIG. 4a and 4b *Electrocardiograms taken 8 years apart in a patient now 18 years old, showing dramatic biatrial hypertrophy, and serially, a diminution in ventricular voltage and development of left bundle-branch block. Clinical features are now those of congestive heart failure. LVEDP 25 mmHg, RVEDP 20 mmHg. No resting gradient was found, but after isoprenaline, a 50 mm gradient developed.*

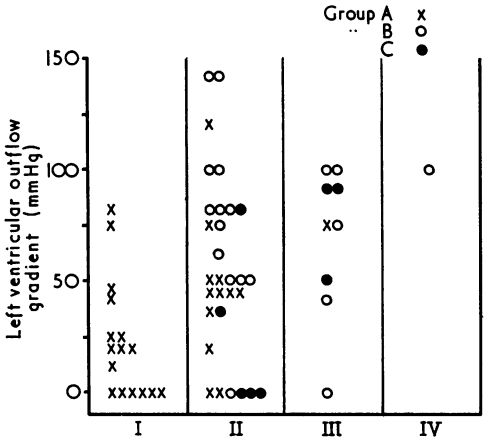


FIG. 5 *Resting left ventricular outflow gradient related to symptom class and progression. A, stable during follow-up; B, improved during follow-up; and C, deteriorated during follow-up.*

none recorded was greater than 40 mmHg. It is probable that these gradients result from Bernheim effect and so represent yet another manifestation of massive septal hypertrophy (Bernheim, 1910).

Angiocardiography *Left ventricular angiograms* were performed in 60 patients, 26 in group A, 22 in group B, and 12 in group C. In our earlier studies biplane angiograms were performed; later cineangiography was used. In all patients the typical angiocardiographic appearance of septal hypertrophy, diminished ventricular end-systolic volume, reflecting systolic outflow tract obstruction, and papillary muscle hypertrophy, were found in varying degrees (Cohen *et al.*, 1964; Grant *et al.*, 1968). We believe that mitral regurgitation plays an important role in hypertrophic obstructive cardiomyopathy (Oakley *et al.*, 1967; Pridie and Oakley, 1970), and this was searched for in all angiograms. In group A, it was found in 18 patients (69%), 4 asymptomatic patients and 14 patients with Class II symptoms. It was judged to be mild in 17 and moderate in 1. In group B, it was present in 15 patients (67%) being mild in 10 patients, moderate in 3, and severe in 2. It was present in 9 patients in group C (75%) and was mild in 5 patients, moderate in 3 patients, and severe in 1 patient. Severe mitral regurgitation was found in 3 patients, 2 with grade III disability and one with grade IV disability. Two of the patients have improved symptomatically. It is probable that the incidence of mitral regurgitation is even higher, for slight degrees cannot be detected on biplane angiograms. Subsequent experience suggests that it is always present when there is an outflow gradient but may be absent when there is not (Goodwin, 1970).

TABLE 5 *Haemodynamic and angiographic data in groups A, B, and C*

		Group A		*Group B*		*Group C*	
Average LV gradient (mmHg)	Class I	22	(17)*	—	—	—	—
	Class II	47	(15)*	70	(16)*	28	(6)*
	Class III	75	(1)*	63	(5)*	77	(3)*
	Class IV	—	—	100	(1)*	—	—
	Total	36±31	(33)*	70±38	(22*)	43±35	(9)*
Average LVEDP	Class I	14·5	(15)*	—	—	—	—
	Class II	16·1	(13)*	18·0	(14)*	19·4	(6)*
	Class III	35	(1)*	27·4	(5)*	24	(3)*
	Class IV	—	—	25	(1)*	—	—
	Total	15·9	(29)*	20·4	(20)*	20·8	(9)*
Average RV gradient		30±17	(10)*	27±15	(7)*	25	(1)*
LV angiogram	Number	26	—	22	—	12	—
	MI absent	8	(30%)	7	(33%)	3	(25%)
	MI mild	17	(64%)	10	(42%)	5	(40%)
	MI mod.	1	(6%)	3	(15%)	3	(25%)
	MI severe	—	—	2	(9%)	1	(8%)

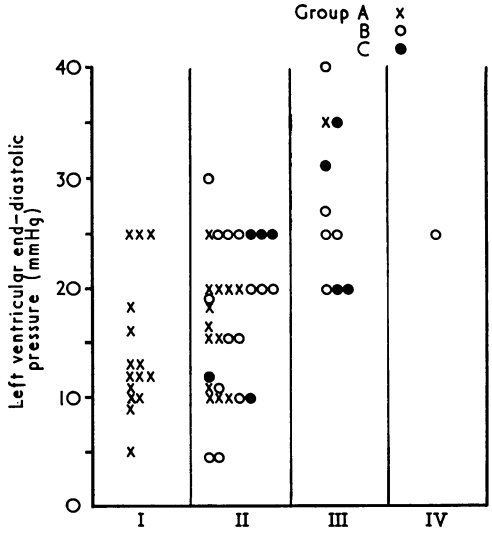
* Number of patients in each category.

Comparison of familial and sporadic patients

The comparison between sporadic and familial patients is of only very limited significance because of lack of access to all relatives or their records in all instances.

Excluding surgical deaths (6), we have a group of 65 'sporadic' and 14 'familial' patients. The clinical profile of the two groups was remarkably similar, with no real difference in disability, and their subsequent fate was also similar. In each group about 50 per

FIG. 6 *Left ventricular end-diastolic pressure related to symptom class and progression (groups as in Fig. 5).*



cent remained stable, 25 per cent improved, and another 15 per cent deteriorated.

Sudden death occurred in one familial patient (7·7%) and in 5 sporadic patients (7·7%).

There were no differences in the electrocardiograms in the two groups. The common abnormalities of ventricular hypertrophy, and Q wave patterns of septal hypertrophy occurred with equal frequency.

The average left ventricular gradient in 55 sporadic patients and 13 familial patients was not statistically different.

The average left ventricular end-diastolic pressure in 53 sporadic patients was 16·4 mmHg and in 11 familial patients 22·8 mmHg. The disparity in the number in each sample makes these figures difficult to compare. This difference occurs in the absence of any other difference in age, sex, or haemodynamics.

Sudden death

Six patients, 5 sporadic and 1 familial, died suddenly during the course of follow-up (Table 6). Five came to necropsy which confirmed the diagnosis. Two of the patients were originally asymptomatic, 3 had Class II disability, and 2 had Class III disability. The average age of onset was 17·0 years and the average age at death was 25·5 years, though there was a wide range for both figures. Four were under 20 years when diagnosed. In 3 patients the interval between onset and death was under 5 years.

Of the 4 who were symptomatic, all complained of dyspnoea. Only 2 complained of palpitations, and of these, only one had frequent attacks of syncope. The other had one attack of syncope before death. Only 2 patients had shown evidence of deterioration before death. The others were in a stable condition.

Two patients had persistent arrhythmias shown on serial electrocardiograms. One had multiple nodal ectopics as the only abnormality on each of several graphs taken over several months, the other developed atrial fibrillation shortly before death. Though this was associated with symptomatic decline, he was still at work and death was unexpected. In all the patients who were in sinus rhythm, the PR interval was normal. Left ventricular hypertrophy was present in 4 patients, complete right bundle-branch block in 1, and incomplete left bundle-branch block in 2 patients.

The patient who had frequent syncopal attacks developed ventricular fibrillation during right heart catheterization, which responded to electrical defibrillation. Though he showed ventricular irritability for some time afterwards, his cardiogram nevertheless became stable before discharge. His death occurred 15 months after that episode.

There was no relation to outflow gradient, the average resting gradient being 47 mmHg, and varying from 0 to 137 mmHg. One patient had a right ventricular gradient of 40 mmHg. However, the left ventricular end-diastolic pressure was high in 4 of the 5 patients in whom it was measured. Subsequent experience suggests that a significant increase in end-diastolic pressure may be the most important feature associated with sudden death.

Pregnancy

A total of 11 pregnancies occurred in 8 women in whom a diagnosis of hypertrophic obstructive cardiomyopathy had been made before

TABLE 6 *Sudden death*

Patient	*Sporadic*	*Sporadic*	*Sporadic*	*Sporadic*	*Sporadic*	*Familial*
Age onset (yr)	4	8	16	30	37	10
Age death (yr)	4	14	26	33	38	33
Class	I	I	III	II	II	II
Syncope	No	No	Yes (I)	No	No	Yes
Course	Static	Static	Static	Deteriorating	Static	Deteriorating
Electrocardiogram findings	LV hypertrophy	LV and RV hypertrophy	Nodal ectopics	Atrial fibrillation, LV hypertrophy, left axis deviation, inferior left bundle-branch block	LV hypertrophy, left axis deviation	LA and RA hypertrophy, RBBB, right axis deviation
LV gradient	20	—	37	0–50	130	48
LVEDP	20	—	9	20	15	30
Necropsy	Yes, hypertrophic obstructive cardiomyopathy	Yes, hypertrophic obstructive cardiomyopathy	Yes, hypertrophic obstructive cardiomyopathy	Yes, hypertrophic obstructive cardiomyopathy	No	Yes, hypertrophic obstructive cardiomyopathy

the onset of pregnancy. We have reported on our experience with 9 women who had between them a total of 13 pregnancies (Turner, Oakley, and Dixon, 1968). Deterioration of symptoms occurred in all these patients. In all except one, the deterioration was of one symptom class. In one patient, who had Class I disability originally, congestive heart failure developed. One patient developed pulmonary oedema after delivery.

Three of the pregnancies were electively terminated in the first trimester. This was in the early years of our experience with obstructive cardiomyopathy, and we now know that it is not usually necessary to recommend termination. There was one spontaneous abortion (in the second trimester) in a woman who has subsequently carried a pregnancy to term and delivered a normal child.

The remainder of the patients proceeded to delivery without serious incident. Patients were treated conservatively with bed rest and diuretics if fluid retention occurred. Propranolol has been given to all recent patients. After delivery, all patients who deteriorated returned to their previous cardiac status. None of the babies of these patients has shown any signs of hypertrophic obstructive cardiomyopathy so far.

Further reviewing the histories of our other women patients, we found 7 additional patients in whom there was a close temporal relation between the initial diagnosis and the birth of the last child. In 7 patients, 15 pregnancies occurred, and in 11 pregnancies in 6 patients, dyspnoea developed during pregnancy, which ranged in severity from Class II to Class III. All the pregnancies, save one, proceeded to term and resulted in a normal infant. The exception was a stillbirth with multiple congenital abnormalities.

Infective endocarditis

Infective endocarditis occurred in 4 of our patients, 3 of whom have already been reported in detail (Vecht and Oakley, 1968). One patient was treated for 6 weeks for endocarditis with intravenous penicillin and was considered cured. He died as a result of a ruptured mycotic cerebral aneurysm, and at necropsy evidence of healed infective endocarditis was found on the mitral valve. The second patient died suddenly in another hospital after a short febrile illness. Blood cultures early in the disease grew pneumococci, and she had developed splinter haemorrhages shortly before death. Her death was quite sudden and did not follow a long period of steadily worsening symptoms. A necropsy was not performed. The third patient was treated successfully for *Staphylococcus albus* endocarditis.

It is probable that infective endocarditis may occur either on the mitral valve, when there is mitral regurgitation, or on the aortic valve in association with outflow tract obstruction.

Therapy

Medical (Table 7) Drugs such as digitalis and isoprenaline which have a positive inotropic effect on the myocardium are well known to increase the systolic pressure gradient in hypertrophic obstructive cardiomyopathy (Braunwald and Ebert, 1962). Experience in acute obstruction has shown beta-adrenergic blockade to block these effects, but not to influence the resting gradient (Goodwin *et al.*, 1964; Flamm, Harrison, and Hancock, 1968).

We have already reported the results of treatment of a small number of patients with this form of cardiomyopathy with long-term beta-adrenergic blockade (Cherian *et al.*, 1966). This study has been expanded, and experience is now available on the treatment of 47 patients treated with propranolol. Initially, the dose of propranolol was 30 mg daily, but more recently larger doses of up to 120 mg daily have been used, and 11 patients have been treated with up to 90 mg a day for 6 months or more. An additional 10 patients have been treated surgically in addition to receiving propranolol and will be included in the discussion of surgical therapy.

Of the 47 patients, 25 were male and 22 were female, their ages ranging from 3 to 55 years; the follow-up has now extended for three years. In evaluating the symptomatic results, we have noted any change in symptom class. Using these criteria, 28 (60%) patients reported no real change in their disability. Six (12%) deteriorated symptomatically and 9 (19%) have shown improvement (Table 7). Many patients reported symptomatic relief of a minor degree, dyspnoea becoming less in 16

TABLE 7 *Long-term treatment with propranolol in 47 patients*

	Symptom class			
	I	II	III	IV
Stable	17	11	—	—
Better	—	6	2	1
Deterioration	—	6	—	—
Dead	—	2	2	—
Total	17	25	4	1

of 31 patients (52%) with this complaint. Angina was reduced in the majority and palpitations in the minority.

Objective evidence of improvement was more difficult to evaluate and was lacking in most patients. There was some relation between symptomatic relief and the haemodynamic state. Angina was relieved more frequently in those patients with an outflow gradient of 50 mmHg or more, and with a left ventricular end-diastolic pressure of less than 15 mmHg.

Four patients died while taking propranolol. One death was from an unrelated preexisting neurological condition in a woman who had been deteriorating. Three others were sudden deaths. One occurred in a familial patient, whose brother had died suddenly in his twenties and who was shown to have hypertrophic obstructive cardiomyopathy at necropsy. The other two were sporadic patients. One further patient had discontinued propranolol 5 months before his death, previously having taken the drug for one year. All 4 of these patients had been taking the drug for less than 18 months.

Surgical Our initial experience in the surgical treatment has already been reported (Bentall *et al.*, 1965). To the original 12 patients, 10 have been added. Sixteen have survived the operation. There were 6 immediate deaths, 3 from complete heart block. Three late deaths have occurred – one, 2 years after operation from a ruptured mycotic cerebral aneurysm secondary to infective endocarditis, one from atrial fibrillation, systemic embolism, and pulmonary oedema, and one suddenly, presumably from arrhythmia.

The criteria for recommending a patient for operation were the presence of significant symptoms, an outflow gradient of at least 50 mmHg, and the angiographic demonstration of a definite obstruction to left ventricular outflow. More recently, the indication for operation has been the failure of such a patient to respond to propranolol therapy.

All the surgical patients had originally presented with at least Class II or III disability, and all had experienced some deterioration before their being recommended for operation. Fourteen of the surviving patients have improved at least one symptomatic class. One patient is unchanged and another has continued to deteriorate despite operation and propranolol.

Both pre- and postoperative haemodynamic data are available for comparison in 12 of the surviving cases. The average preoperative gradient was 81 ± 35 mmHg. The average highest resting gradient after operation was 34 ± 18 mmHg. The gradient fell in all except 2 after operation. One of the patients in whom there was no postoperative change had a gradient of 80 mm before and 90 mm after operation. The other patient showed an increase of 60 mmHg over the preoperative gradient, and in this patient there has been steady deterioration.

Postoperatively, cineangiocardiography has shown very little change from the preoperative appearance. In 5 patients, mitral regurgitation present before had improved or disappeared after operation. These results are less impressive than those of Morrow *et al.* (1968).

It has become our policy to continue propranolol after operation in the surgical patients.

Discussion

Our experience has been similar to that of others (Frank and Braunwald, 1968; Maurice *et al.*, 1966) with respect to the age of the patients and the severity of symptoms.

Progress Patients who remained asymptomatic were significantly younger at the time of detection than those with symptoms, suggesting that the disease commonly had a prolonged asymptomatic period between the development of clinical stigmata of the disease and the development of disability. Detection of the heart murmur may have brought to light symptoms real or imagined in patients who might otherwise have remained undiscovered until they presented at an older age with greater disability. The group C patients can now be seen to represent patients whose murmurs had not been detected during the long latent period before disability became gradually noticeable to them.

During the course of follow-up, we have noted, as have others (Wigle, 1964), a fluctuation in the signs and symptoms from visit to visit, but we have tried to analyse the patients in terms of a general trend. In the symptomatic patients in groups A, B, and C, there was no significant relation between the initial signs and the prognosis. In most of the patients who have shown deterioration, we have noted a gradual diminution of the ejection murmur and a gradual accentuation of congestive or restrictive features, such as added heart sounds, raised jugular pressure dominated by 'a' wave, and pulmonary congestion. We have not noted this change in any patients who have improved or remained stable.

Electrocardiography Electrocardiograms were normal in only 3 of the 85 patients. Evidence of left atrial hypertrophy correlated well with the increase in left ventricular end-diastolic pressure and the presence of symptoms, but its presence did not preclude survival with stability during the period of observation. Left ventricular hypertrophy was present in about 50 per cent of the cases and did not correlate well with the degree of the left ventricular outflow obstruction.

Though the Wolff-Parkinson-White syndrome has been reported in hypertrophic obstructive cardiomyopathy (Frank and Braunwald, 1968), it did not occur in the classical form in our series. PR intervals of less than 0·13 sec were found in 6 patients (all sporadic cases). The PR interval, however, was usually in the lower ranges of normal in our patients (A. Levin, 1966, unpublished data). Others have found a high incidence of WPW in 'familial cardiomyopathy' (Westlake, Cohen, and Willis, 1962).

Deep Q waves mimicking cardiac infarction were seen in 12 of our patients, 9 in group A and 3 in group B. In none was there historically a suggestion of myocardial infarction.

Haemodynamics A number of our patients had no resting left ventricular outflow gradient at any time.

The fact that patients who deteriorated had no resting gradients is interesting. In group C, 3 patients had no measurable resting gradient but left ventricular end-diastolic pressure increased to around 25 mmHg. It appears then that one of the patterns of deterioration in the natural history is the development of inflow obstruction (Oakley, 1971a).

The average resting left ventricular end-diastolic pressure was lowest in group A, as might be expected, since these were the least symptomatic. There was no difference between groups B and C in this regard. Grossly raised pressures occurred in all three groups and in general seemed to correlate with severity of symptoms. The clinical evidence of restriction with resulting pulmonary congestion (indirect evidence of an increased pressure) was impressive in most of the patients who deteriorated.

Right ventricular outflow gradients were found in 37·5 per cent of patients in whom they were sought. There was no difference in its incidence among the groups nor any correlation with symptoms. Lockhart *et al.* (1966) reported 13 patients with hypertrophic obstructive cardiomyopathy in whom right ventricular gradients were also found. In our series, the presence of a right ventricular gradient did not have great clinical significance. We feel that in most instances right ventricular gradients are secondary to massive septal hypertrophy and not due primarily to disease of the right ventricle (Goodwin *et al.*, 1964).

Angiography The angiographic picture is typical (Simon *et al.*, 1967; Cohen *et al.*, 1964; Steiner, 1964) and we accept it as diagnostic in the absence of a gradient. Mitral regurgitation occurred in 70 per cent of our patients, a higher figure than that reported from other authors (Simon *et al.*, 1967; Bourdarias *et al.*, 1968). Minor degrees were not always detected by roll-film angiography, and we now consider that mitral regurgitation is virtually invariable in all patients with outflow obstruction. There was no difference in the incidence of mitral insufficiency among groups A, B, and C.

Familial incidence and sudden death The incidence of familial patients is less than that reported by Frank and Braunwald (1968). Many familial patients were undoubtedly inadvertently classified as sporadic because of lack of proof to the contrary. A history of relatives dying suddenly at an early age in many of our sporadic patients strengthens the impression that the true incidence of sudden death is probably greater in familial than sporadic patients. A family reported by us (Hollman *et al.*, 1960) had a high incidence of sudden death and we have subsequently noted this in other families not included in this analysis. Reports of the clinical severity in familial patients vary (Frank and Braunwald, 1968; Wigle, 1964), but in our series there was no difference in disability or prognosis. Sudden death is a prominent feature in many reports of familial cardiomyopathy (Brent *et al.*, 1960; Horlick, Petkovich, and Bolton, 1966; Paré *et al.*, 1961).

There are few clinical clues to the detection of the person prone to sudden death. Two of our patients had been asymptomatic. There was no distinctive electrocardiographic or haemodynamic features which would distinguish these patients except a high left ventricular end-diastolic pressure. Syncope, which occurred in two, may be considered an ominous sign. The mechanism causing sudden death is unknown, but the most likely initiating factor is tachycardia or arrhythmia because left ventricular filling is slow in this disease.

Pregnancy Though there is a tendency for an increase in symptoms during pregnancy,

there seems to be no added risk of permanent harm to the mother or child. None of our patients had greater than a Class II disability at the onset of pregnancy and in fact more than half were asymptomatic. We now feel that pregnancy can usually be safely carried to term.

Atrial fibrillation Atrial fibrillation causes significant deterioration in hypertrophic obstructive cardiomyopathy. The atrial gallop rhythm and palpable atrial contraction signify increased inflow resistance with reduced ventricular compliance and this sets the stage for atrial fibrillation. Three of our four patients had clinical and haemodynamic evidence that inflow obstruction rather than outflow obstruction had become the major haemodynamic fault.

Infective endocarditis The addition of our three cases complicated by infective endocarditis to those reported by Vecht and Oakley (1968) brings the total of reported cases to 16 (Boiteau and Allenstein, 1961; Frank and Braunwald, 1968; Linhart and Taylor, 1966; Soulié, Jocy, and Carlotti, 1962). In previously reported cases, there has been a good response to the appropriate antibiotic therapy. However, death occurred in 2 of our patients. Three of the 16 reported patients had had dental manipulation immediately before the onset of infection, and this underlines the need for antibiotic prophylaxis in patients with hypertrophic obstructive cardiomyopathy.

Treatment Because of the lack of previous information concerning the untreated natural history of large numbers of patients with hypertrophic obstructive cardiomyopathy, it is hard to assess our results with medical therapy propranolol. The objective results of the long-term use of the drug are somewhat unimpressive, though the trend is encouraging. Its use has been associated with a lack of progression of or development of symptoms in most cases. There has been substantial improvement in a few. The most important indication for its use would be the demonstration of the prevention of sudden death. In addition, the relief of angina and diminution of arrhythmia are important factors. The effect of beta-adrenergic blockade on ventricular function is under study, and preliminary work suggests that it can reduce cardiac work and lower left ventricular diastolic pressure on effort (Edwards *et al.*, 1970; Goodwin, 1970; Webb-Peploe *et al.*, 1971).

Surgery may continue to play a role in the treatment of some patients despite the use of propranolol. Lowering the ventricular outflow tract and symptomatic improvement in surviving cases has been the experience of most groups (Bigelow *et al.*, 1966; Morrow *et al.*, 1968).

A unifying concept

Our observations on the natural history of the disease appear to support the following unifying concept.

The initiating mechanism remains obscure. The presence of mitral insufficiency and papillary muscle hypertrophy in a large percentage of the cases has led us to believe that abnormal papillary muscle function is an important factor in the development of hypertrophic obstructive cardiomyopathy (Oakley *et al.*, 1967; Goodwin, 1967). Abnormal contraction of the papillary muscles could result in their abnormal apposition to the hypertrophied septum, initiating or intensifying outflow obstruction. This might be followed by a vicious circle of more hypertrophy, further regurgitation, and further obstruction (Goodwin, 1970).

Robb and Robb (1942) pointed out that if the deep bulbospiral muscle of the left ventricle contracted prematurely, it would cause aortic outflow obstruction by a mechanism of septal hypertrophy.

Some mechanism, perhaps abnormal growth of muscle, initially causes a disorder of myocardial contraction, characterized by the rapidity and completeness of ventricular emptying. Initially, the disease is asymptomatic or only mildly symptomatic, and tends to run a stable course. It is characterized by septal hypertrophy, outflow obstruction, and mitral regurgitation. At this point, there is usually already some increase in end-diastolic pressure. Symptoms when they develop are due to high left atrial pressure (dyspnoea) and to increased cardiac work and myocardial oxygen demands (angina).

The condition may seem to remain static or worsen depending on the segment of the natural history which is observed. Inflow resistance tends to increase, and is due to massive hypertrophy and varying degrees of replacement fibrosis. Outflow obstruction may disappear and in some patients may never have been present (Oakley, 1971b; Goodwin, 1970).

It is possible that the cause of the disease may be modified at this point by beta-adrenergic blockade, and in some patients by operation. As yet there is no proof that either method of treatment will certainly prevent progression, however. Important inflow resistance is manifested by diminution of the sys-

tolic murmur, accentuation of gallop rhythm, raised jugular venous pulse with prominence of the 'a' wave, and, finally, atrial fibrillation and congestive cardiac failure. Haemodynamically, atrial fibrillation is associated with reduction in the left ventricular outflow gradient and an increase in left ventricular diastolic pressure. Embolism may occur (Oakley, 1971a; Goodwin, 1970).

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