

Cardiac Function in Primary Myocardial Disorders*—Part I

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[WITH SPECIAL PLATE]

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The term cardiomyopathy has become accepted as a suitable designation for disorders of heart muscle of unusual or unknown cause. The following definition, slightly modified from that suggested by Goodwin *et al.* (1961), is suggested: "Cardiomyopathy—an acute, subacute, or chronic disorder of heart muscle of unknown or obscure aetiology often with associated endocardial or sometimes with pericardial involvement but not atherosclerotic in origin."

The term "primary myocardial disorder" denotes those cardiomyopathies that involve the myocardium primarily, and do not result from disease in other parts of the heart, such as the valves or coronary arteries, or from diseases elsewhere in the body, and I shall not deal with conditions such as haemochromatosis, diffuse systemic sclerosis, disseminated lupus erythematosus, sarcoidosis, polyarteritis nodosa, or amyloid disease, which, when they involve the heart, do so as part of a general system disease.

It has already been suggested (Goodwin *et al.*, 1961) that cardiomyopathies may present clinically in more than one way: as congestive, constrictive, or obstructive types respectively.

Clinical Material and Methods

This lecture describes the disorders of structure and function in 48 patients with cardiomyopathy studied at the Postgraduate Medical School of London and Hammersmith Hospital. The patients have been divided into four groups according to their clinical and angiographic characteristics: (1) congestive cardiomyopathy (eight patients); (2) constrictive cardiomyopathy (five patients); (3) hypertrophic obstructive cardiomyopathy (29 patients); and (4) unclassified group (having features common to one or more of the other groups (six patients).

Only patients who have been studied by cardiac catheterization or angiocardiography have been included. Haemodynamic or angiographic investigations have been impracticable in many patients, who are therefore not presented, while in others the treacherous nature of the disease has prevented complete investigation.

The omission from the list of important conditions such as endomyocardial fibrosis and of cardiomyopathy associated with pregnancy or the puerperium is due solely to lack of sufficient personal experience in studying these important conditions.

I shall seek to show how the differences in structure and function in the various types may influence the clinical presentation and offer clues to aetiology, and to the disordered physiology.

Congestive Cardiomyopathy

The right atrial pressure was elevated in all but two of the eight patients, the maximum mean pressure being 18 mm. Hg. Pulmonary artery pressures were normal or only slightly

elevated, the maximum systolic pressure being 40 mm. Hg. Systolic gradients between the right ventricle and the pulmonary artery were minimal or absent. The right ventricular diastolic pressure was less than 10 mm. Hg in five of the six patients and the maximum was 12 mm. Hg (in one patient). The level of diastolic pressures was thus consistent with heart failure without serious impairment to ventricular filling. The mean indirect left atrial pressure measured by wedging the cardiac catheter in a terminal branch of the pulmonary artery (pulmonary "wedge" pressure) was elevated in only one patient, in whom it was 18 mm. Hg (Fig. 1).

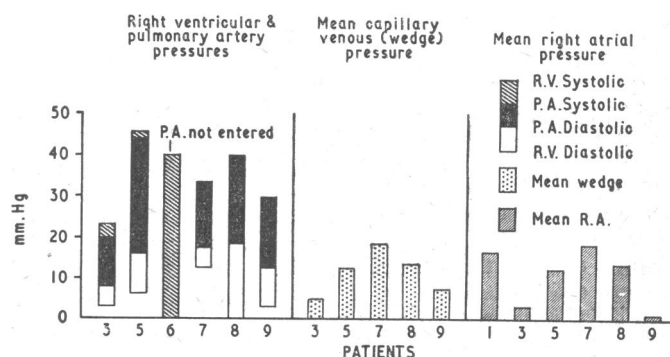


FIG. 1.—Haemodynamics in the congestive type of cardiomyopathy.

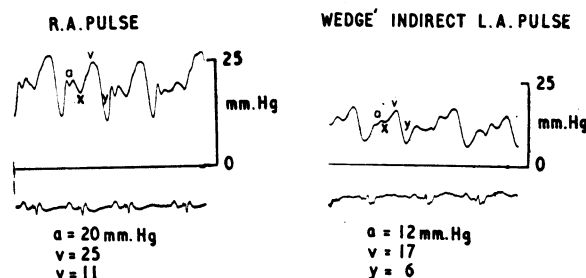


FIG. 2.—Right atrial (RA) and "wedge" indirect left atrial pulse (LA) in congestive cardiomyopathy.

Right atrial and indirect left atrial pressures are shown in Fig. 2 and have a similar form, though the right atrial pressure is higher than the left. The poor "x" descent indicated tricuspid incompetence, which is common in these patients, and the form of the left atrial pulse suggested functional mitral incompetence also. The steep "y" descent confirmed absence of atrio-ventricular valvar obstruction. The cardiac output was low or low normal in every patient, never exceeding 5 l./min. The pulmonary vascular resistance was normal.

* This is a slightly abridged version of the tenth Strickland Goodall Lecture delivered at the Apothecaries Hall on 30 October 1963.
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These results suggest poor contractile function such as might be expected from a flabby and dilated heart. Further evidence of poor myocardial function is demonstrated by the electro-

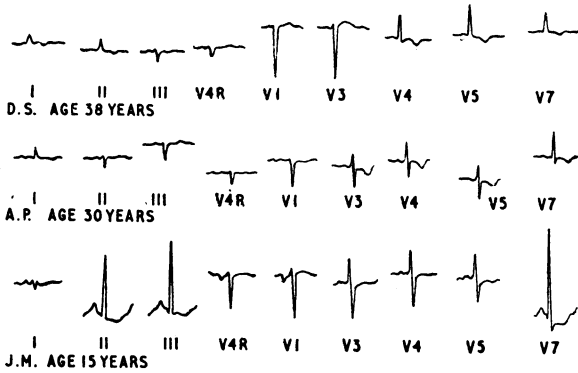


FIG. 3.—Electrocardiograms in three patients with congestive cardiomyopathy. Low voltage QRS complexes, poor R waves in left pre-ordial leads (with the exception of V₁ in patient J.M.), and flat or slightly inverted T waves indicate a myocardium of poor quality.

cardiogram, which shows left bundle-branch block or low-voltage complexes with inverted or flat T waves, indicating myocardial disorder (Fig. 3), as has been shown by Hollister and Goodwin (1963). Atrial fibrillation occurred in five of the eight patients.

Radiology of the heart showed considerable cardiomegaly.

Angiocardiography confirmed enlargement of the chambers without increased thickness of the ventricular wall, indicating little hypertrophy. In every case studied the circulation time was slower than normal, being consistent with reduced cardiac output. There was no evidence of any obstruction to inflow or outflow (Special Plate, Fig. 1).

These investigations suggested a dilated heart with a poor myocardium and little hypertrophy. This impression was borne out by two patients who died and whose hearts were dilated and overweight. In neither was there any diagnostic abnormality on histological examination, and in one the muscle appeared normal. The dilated and flabby myocardium would readily explain the frequent tendency to congestive heart failure, atrio-ventricular valve incompetence, gallop rhythm, and atrial fibrillation in such patients.

An infective origin seems a possibility, but round-cell infiltration might be expected, as has been described in epidemic primary myocarditis in children (Freundlich *et al.*, 1958), and in virus myocarditis (Pearce, 1960). Though the histology was negative on routine examination in the two fatal cases in this series, my colleagues and I have previously reported round-cell infiltration in the myocardium in congestive cardiomyopathy (Goodwin *et al.*, 1961), and it seems possible that in many patients this clinical type of cardiomyopathy may be due initially to an infective cause, possibly viral in nature. Many viruses could be implicated, and Pearce (1960) has shown that a reduced myocardial oxygen supply determines the involvement of the heart rather than the type of virus. Virus studies in all the patients reported here were negative, but in one patient toxoplasmosis may have been the cause of the cardiomyopathy. Hypersensitivity must also be considered as a possibility, and has been described in the elderly by Kline *et al.* (1963), but eosinophilia in life has been a feature in only one patient in the present series, and has not been found in the hearts that were studied at necropsy. Clearly other factors may be at work, and elucidation may depend on more refined techniques such as electron microscopy and enzyme studies of the myocardium.

Constrictive Cardiomyopathy

In my experience this is often due to infiltration of the myocardium with some process that renders it rigid and unyielding.

Thus, out of 11 cases seen by me personally, four were due to primary amyloid disease, one to polyarteritis nodosa, and one to extreme infiltration with leukaemic cells. In these cases endocardial involvement was common, contributed to the rigidity of the ventricles, and hence accounted for the similarity to constrictive pericarditis and right-sided endomyocardial fibrosis. Furthermore, infiltrating processes such as amyloid may affect the pericardium also.

The five patients with constrictive cardiomyopathy considered in this lecture, however, did not have any disease elsewhere, and must be regarded as having a primary myocardial disorder. In these patients, right atrial pressures were usually slightly higher than in the congestive group. Tricuspid incompetence was absent, a sharp “x” descent being present, and a “y” descent of variable size also being seen in the right atrial pulse (Figs. 4 and 5). In one patient the right atrial pressure rose on inspiration as noted in patients with primary amyloid disease of the myocardium (Brigden, 1957; Goodwin *et al.*, 1961).

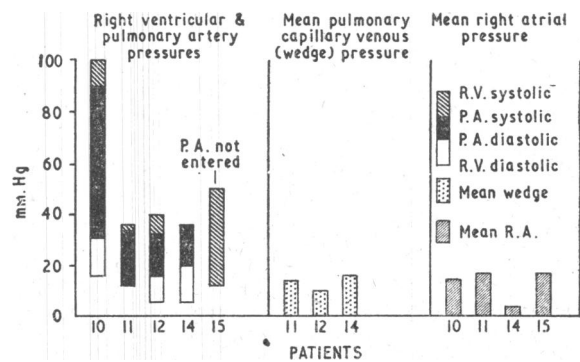


FIG. 4.—Haemodynamics in constrictive cardiomyopathy.

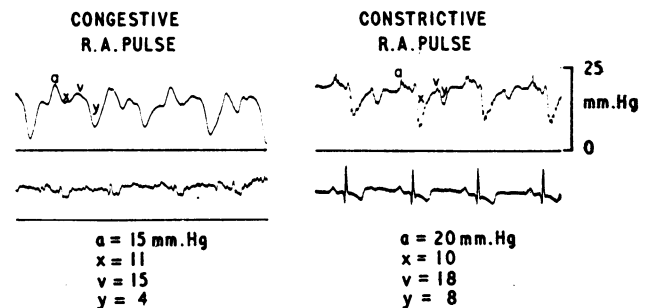


FIG. 5.—Right atrial pressure pulses in two patients with constrictive and congestive cardiomyopathy. The sharp “x” descent and high “v” wave in the constrictive type contrast with the poor “x” descent due to tricuspid incompetence and the lower “y” descent in the congestive type.

Right ventricular systolic pressures were slightly higher than in the congestive group in four patients, and severe pulmonary hypertension was present in one, whose systolic pulmonary artery pressure was 90 mm. Hg. Gradients between right ventricle and pulmonary artery were trivial (Fig. 4). By contrast right ventricular diastolic pressures were higher than in the congestive group, the minimum being 6 mm. Hg and the maximum being 16 mm. Hg, while none were at zero level. “Wedge” pulmonary artery pressures were barely elevated (Fig. 4), and the cardiac output with one exception was low. Thus the haemodynamics in these patients did not differ greatly from those in the patients with congestive cardiomyopathies apart from the form of the right atrial pulse and the slightly greater right ventricular end-diastolic pressures. Though the heart tended to be smaller in size (Special Plate, Fig. II) angiocardiograms were notable for lack of evidence of hypertrophy and of obstruction, and in one patient showed an unexpectedly small right ventricular cavity. The absence of pericardial thickening served to differentiate these patients from those with constrictive pericarditis.

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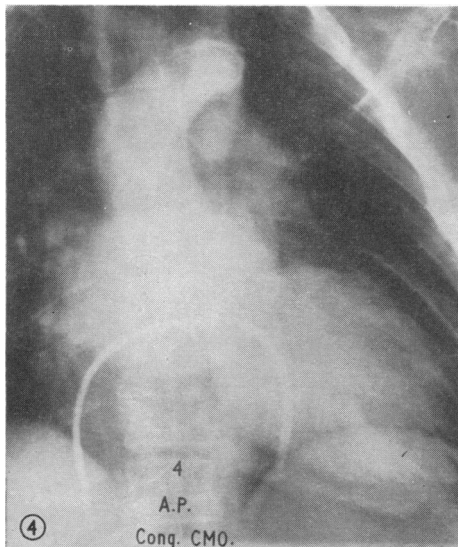
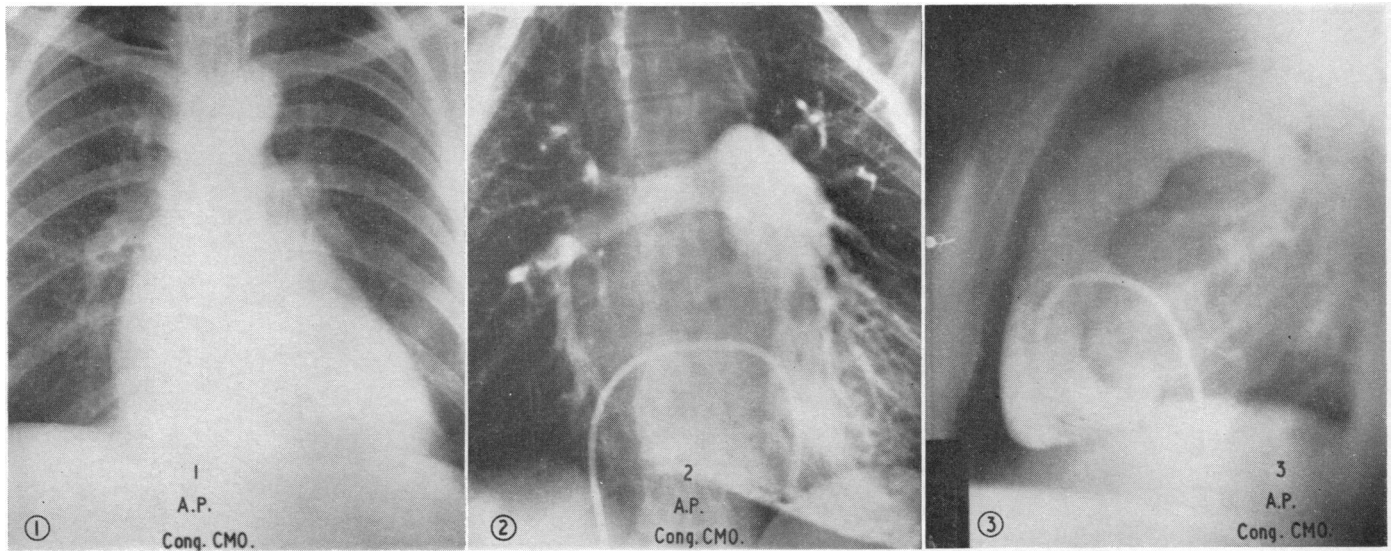


FIG. I. — Angiocardiographic studies in a patient with congestive cardiomyopathy.

- (1) Six-foot postero-anterior chest film showing generalized cardiac enlargement.
- (2) Right ventricular angiograms showing large thin-walled right ventricle (antero-posterior projection).
- (3) The lateral projection shows that there is no obstruction to flow through the infundibulum of the enlarged right ventricle.
- (4) The left atrium and left ventricle are enlarged but there is no obvious hypertrophy of the left ventricular muscle.

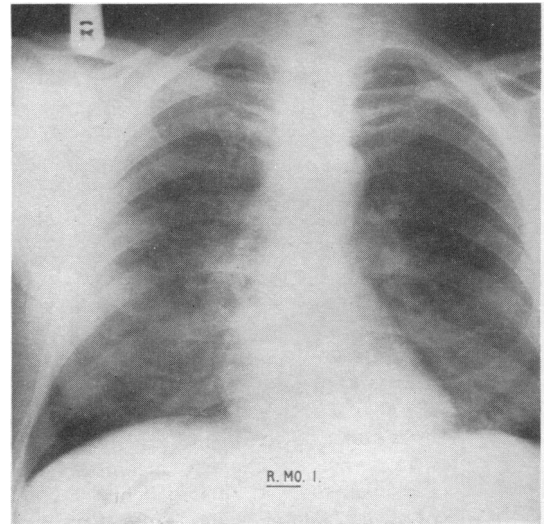


FIG. II.—Six-foot postero-anterior radiograph of the chest in constrictive cardiomyopathy showing little or no cardiac enlargement.

FIG. II

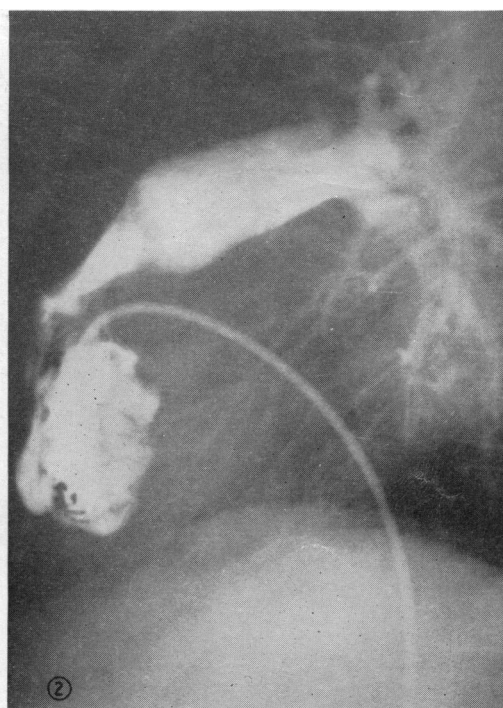
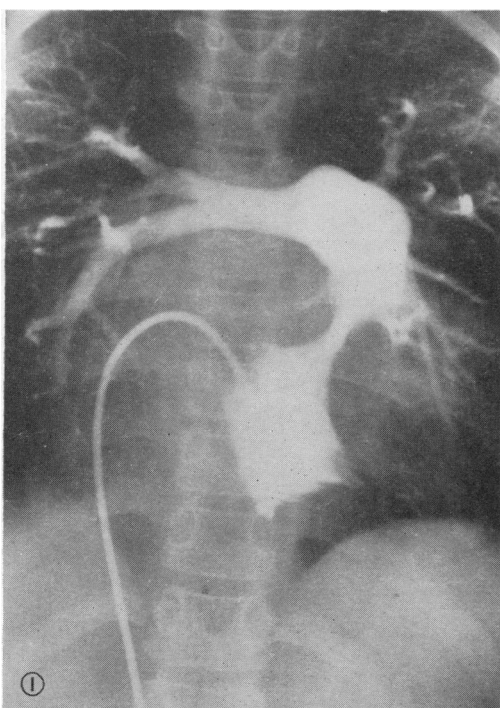


FIG. III.—Right ventricular angiocardiogram in a patient with hypertrophic obstructive cardiomyopathy.

- (1) Antero-posterior projection showing hypertrophied ventricular septum encroaching on outflow tract.
- (2) Lateral projection showing encroaching of outflow tract by irregular masses of hypertrophied muscle.

The pulmonary valve is normal.

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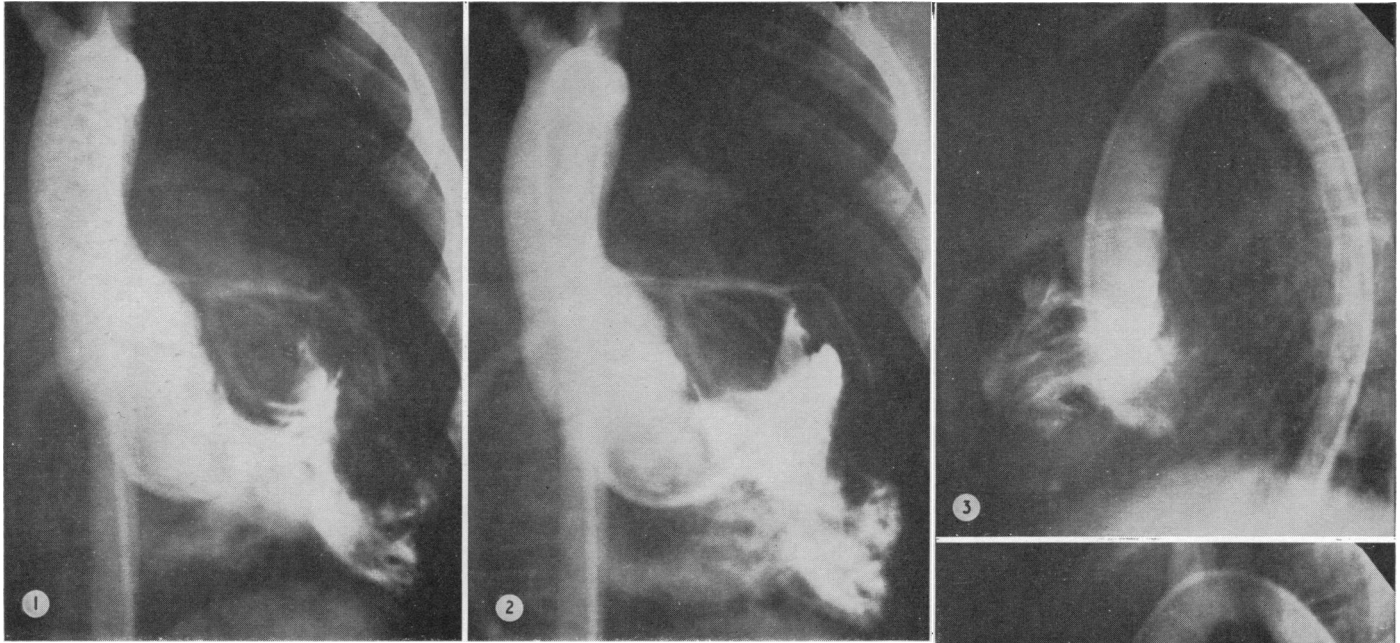


FIG. IV.—Left ventricular angiograms in hypertrophic obstructive cardiomyopathy.

- (1) Antero-posterior projection: systolic film, showing hypertrophied muscle encroaching irregularly on the cavity of the left ventricle.
- (2) Antero-posterior projection: diastolic film showing persistent encroachment of cavity by muscle masses.
- (3) Lateral projection: systolic film showing grossly hypertrophied muscle and encroachment of cavity, with narrowing of outflow tract towards the apex of the ventricle, well below the aortic valve.
- (4) Lateral projection: diastolic film showing coning of the outflow tract.

The coronary arteries, aortic valve, and aorta are normal. No mitral incompetence occurred in this patient.

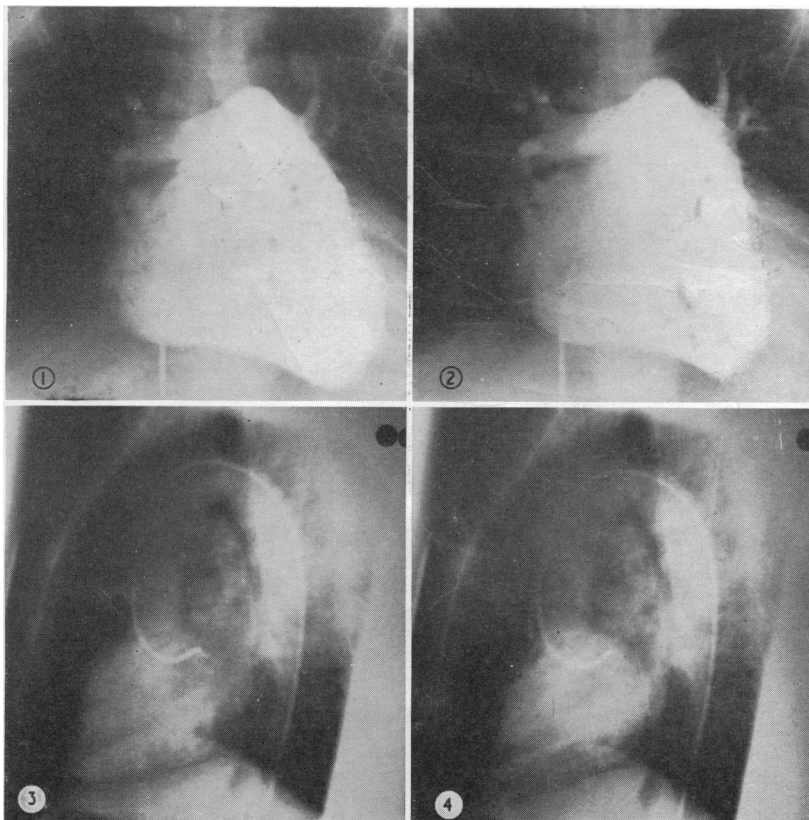


FIG. V.—Unclassified group: right ventricular angiograms (1 and 2) in the postero-anterior projection, showing large right ventricle with little difference between systolic (1) and diastolic (2) volumes, and no bulging of the septum into the right ventricular cavity. Left ventricular angiograms (3 and 4) showing also little variation in cavity volume. There is enlargement of the ventricle but no obstruction or obvious muscular hypertrophy. Ectopic beats did not account for lack of changes in cavity volume.

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FIG. VI.—*Unclassified group*: left ventricular angiogram (trans-septal route) showing large left ventricle without obstruction or hypertrophy and little difference between systolic (left) and diastolic (right) volumes. The left atrium is small and there is a slight degree of aortic coarctation.

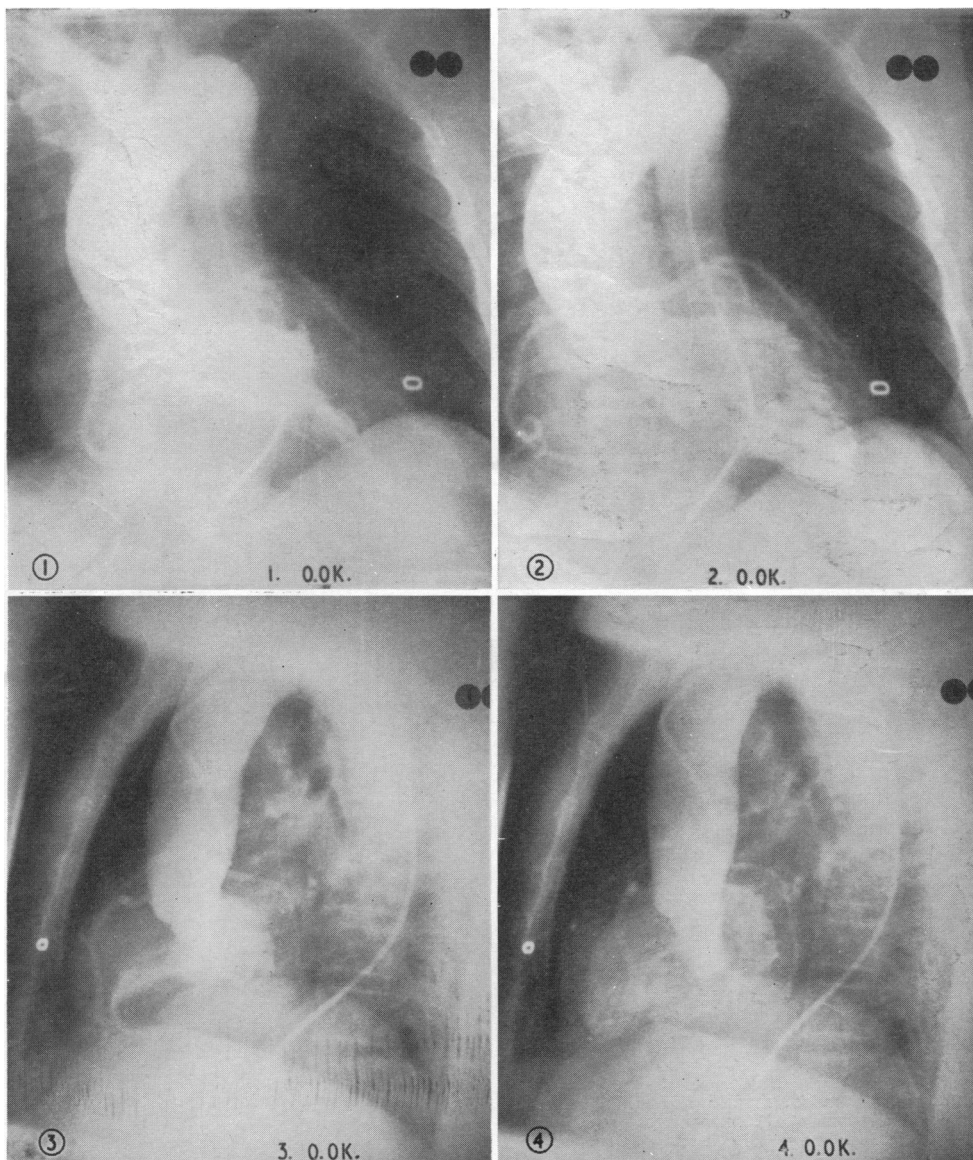
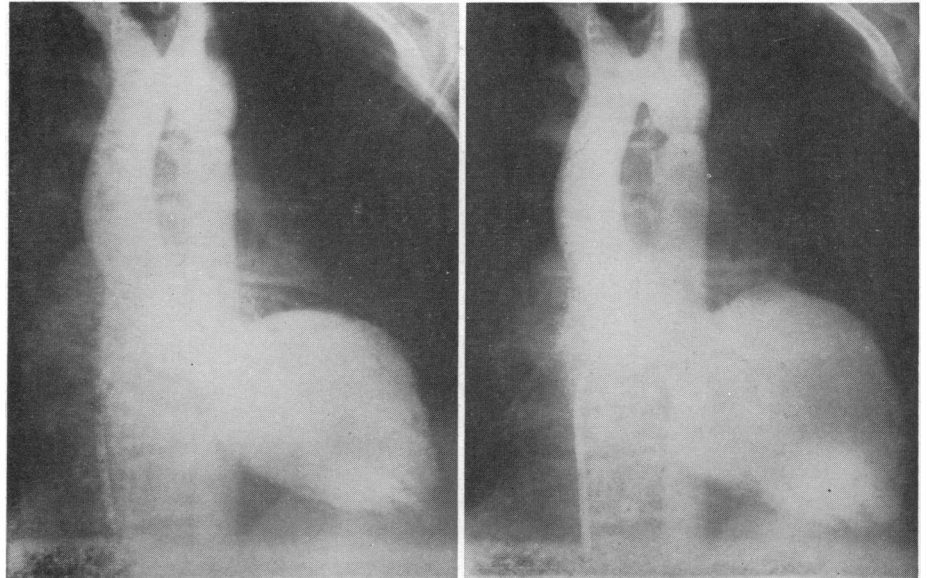


FIG. VII.—*Unclassified group*: left ventricular angiograms. Antero-posterior projection (1 and 2). Lateral projection (3 and 4). There is considerable muscular hypertrophy and slight narrowing of the outflow tract resembling that seen in hypertrophic obstructive cardiomyopathy, but no obvious obstruction to outflow. Appreciable difference between systolic and diastolic volumes is seen, but there is no mitral reflux. The coronary arteries are normal.

The electrocardiogram was similar to that in the previous group, except that atrial fibrillation was present in only one of the four patients. A tendency for the duration of systole (QT_c) to be shorter in the constrictive than the congestive group has been reported (Hollister and Goodwin, 1963).

It is apparent that while there may be clear-cut differences between congestive and constrictive cardiomyopathy the two groups can merge into one another, the differences depending on the ability of the myocardium to yield fully in diastole. Many factors are probably concerned in the exact haemodynamic presentation, including the elasticity of the myocardium, the amount of fibrosis, the degree of involvement of the heart, and the presence or absence of endocardial disease. Indeed, during the course of cardiac illness in cardiomyopathy I have seen a patient pass from the constrictive into the congestive phase. It must also be remembered that a high right ventricular diastolic pressure and a low right ventricular pulse pressure are signs not merely of restricted diastolic function but also of heart failure, whatever the cause. Fig. 6 illustrates the similarity in right ventricular pulse form that sometimes occurs in congestive and constrictive cardiomyopathies respectively, and also shows the transmission of the "a" wave to the ventricular pulses in the former, indicating how the function of the atrium may aid that of the ventricle.

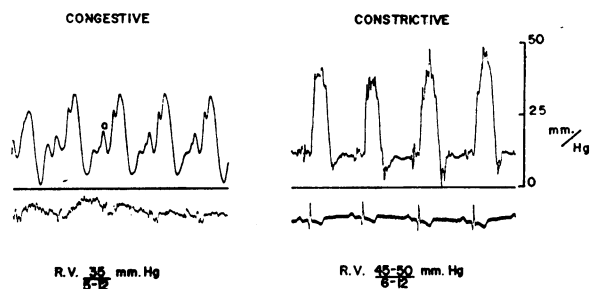


FIG. 6.—Right ventricular pressure pulses in two patients illustrating the similarity that may occur between congestive and constrictive cardiomyopathy.

It seems probable that florid signs of constriction are due usually to infiltration by pathological material (usually primary amyloid), while less severe syndromes which may shade into the congestive type could be due to infection.

Hypertrophic Obstructive Cardiomyopathy

The first clue to this interesting condition was provided by Sir Russell Brock, who, in 1957, described functional obstruction of the left ventricle in a patient with a gradient between left ventricle and aorta due to a large mass of hypertrophied ventricular muscle, thought to be the result of systemic hypertension. Since then a number of reports have appeared describing patients with gross left ventricular hypertrophy obstructive outflow under titles such as "pseudo aortic stenosis" (Bercu *et al.*, 1958); "functional aortic stenosis" (Morrow and Braunwald, 1959); "muscular subaortic stenosis" (Brent *et al.*, 1960); "familial hypertrophic subaortic stenosis" (Brockenborough *et al.*, 1961; Boiteau and Allenstein, 1961); "diffuse subvalvular aortic stenosis" (Kirklin and Ellis, 1961); "functional sub-aortic stenosis" (Brachfeld and Gorlin, 1961); and "muscular sub-aortic stenosis" (Wigle *et al.*, 1962; Wigle, 1963).

Teare (1958) described a condition of asymmetrical hypertrophy of the heart, in which generalized cardiac hypertrophy was associated with massive bulging of the septum into both ventricular cavities leading to obstruction of the inflow and outflow of blood. In 1960, my colleagues and I, in conjunction with Teare, described the clinical syndrome in eight patients who presented with signs of obstruction to left ventricular outflow mimicking aortic stenosis (Goodwin *et al.*, 1960). We

also (Hollman *et al.*, 1960) described a family suffering from the same condition with signs of obstruction to right ventricular inflow. These papers suggested that these conditions were due to a generalized disorder of heart muscle which at that time was described as "obstructive cardiomyopathy" in the belief that the emphasis on sub-aortic stenosis was misleading, since obstruction could occur to the right ventricle also. Recently, in view of further experience, we have added the term "hypertrophic" to the definition (Cohen *et al.*, 1964).

The clinical features are well recognized. Symptoms include syncope and angina on effort or at rest, while sudden death may occur. Dyspnoea is not uncommon, but congestive heart failure unusual. The clinical signs are a jerky arterial pulse with a sharp percussion wave and a marked tidal wave; a late ejection systolic murmur, maximal at the left sternal edge often with a thrill, and a double apical impulse. In some cases an apical pan-systolic murmur suggesting mitral incompetence occurs. The heart is often globular in shape, the aorta is not enlarged, and there is no calcification of the aortic valve. Electrocardiography shows biventricular and biatrial hypertrophy. When there is obstruction to ventricular inflow there may be mid-diastolic murmurs, an augmented "a" wave in the jugular venous pulse, and atrial gallop. A familial incidence of around 20% has been noted by us and by other workers. The condition may apparently occur at any age and is likely to be progressive (Goodwin *et al.*, 1960; Cohen *et al.*, 1964).

Haemodynamic and Angiographic Studies

My colleagues and I have now studied 29 patients by right and left ventricular angiography and catheterization, our results having been published elsewhere in full (Cohen *et al.*, 1964). In this lecture I shall compare and contrast the results with the other types of cardiomyopathies.

Left Heart Catheterization.—This revealed, as in other series, variable, but often considerable, systolic pressure gradients between the left ventricle and the aorta (Fig. 7). But, as will be seen, four patients had no gradient at the time of catheterization while four others had small gradients only. These gradients, moreover, varied from time to time in the same patients, as did the intensity of the obstructive murmur (Goodwin *et al.*, 1961; Cohen *et al.*, 1964).

The left ventricular pressure pulse usually had a smooth upstroke and a sharp downstroke, but often there was an interruption on the upstroke at the time when obstruction occurred, and a striking feature was the elevation of the left ventricular end-diastolic pressure; in 17 of 25 patients this exceeded 25 mm. Hg. This elevation of left ventricular end-diastolic pressure did not bear any relation to the magnitude of the outflow gradient or to the left ventricular systolic pressure.

The gradients were found well below the aortic valve, usually between the body of the ventricle and the subvalvar region

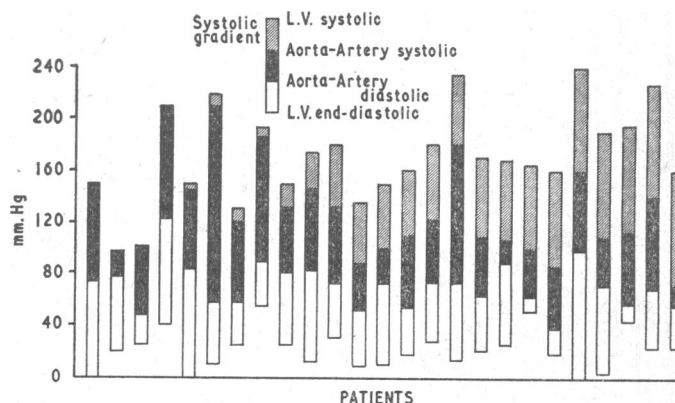


FIG. 7.—Data from left heart catheterization in 25 patients with hypertrophic obstructive cardiomyopathy.

(Fig. 8). The "a" wave of the left atrial pressure pulse could frequently be seen on the ascending limb of the left ventricular pressure pulse, indicating the help given to the left ventricle by the left atrium. In three patients ventricular alternans was present. The sharp descending limb of the ventricular pulse indicated that ventricular relaxation was not impaired. The end-diastolic pressure was consistently elevated, suggesting resistance to filling.

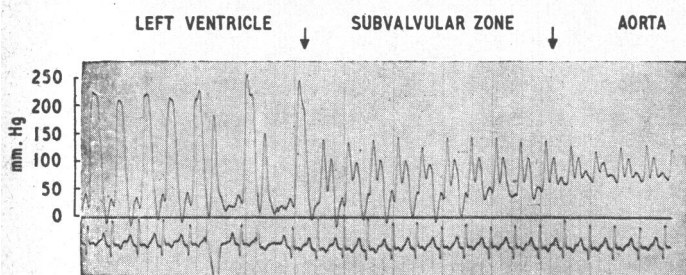


FIG. 8.—Withdrawal trace from left ventricle to aorta in a patient with hypertrophic obstructive cardiomyopathy. The "a" wave from the left atrium can be seen transmitted to the left ventricular pressure pulse, and the gradient between the left ventricle and aorta lies well below the aortic valve. The sharp down-stroke suggests that the relaxation time of the ventricle is normal. (Reproduced by courtesy of the Editor, *British Heart Journal*.)

Retrograde Left Ventricular Angiocardiology.—In 25 patients this revealed hypertrophy of the left ventricle. Mitral incompetence was demonstrated in 10 (40%), and ciné-angiography in three showed that it occurred late in systole. The main abnormalities that were seen affected the body of the left ventricle and the left ventricular outflow tract respectively. These were most striking in systole, but also present in diastole. Increased thickness of the left ventricular wall was present in all, and in systole the cavity of the left ventricle was encroached on by muscle of the septum, base of the heart, and of the left cardiac border. In diastole the size of the left ventricle often appeared to be restricted.

Irregular areas in the ventricle due to masses of hypertrophied muscle bulging into the cavity were common. There were also pockets of contrast medium seen in the ventricular muscle. In 20 patients an inverted cone-shaped area was seen in the left ventricular outflow tract below the aortic valve, and was most marked in diastole. This feature, together with the irregular masses of muscle encroaching on the left ventricular cavity, formed the pathognomonic angiographic appearances of the disorder and permitted a definite diagnosis. The left ventricle failed to open fully in systole owing to the constriction between the body of the left ventricle and subvalvar region (Special Plate, Fig. IV).

In five patients, however, there was no definite outflow tract obstruction and no gradient, but the appearances otherwise were the same as in the other patients.

The coronary arteries and aortic valve appeared normal and there was no dilatation of the ascending aorta.

These appearances are entirely different from those of cardiac hypertrophy from other causes, such as aortic stenosis. In true aortic stenosis the irregular masses of muscle encroaching on the ventricular cavity and the pockets of contrast medium are not seen. There is full excursion in the size of the left ventricular cavity in systole and diastole, and there is no cone-shaped subvalvar narrowing persisting in diastole (Cohen *et al.*, 1964).

Failure to pass the catheter deep enough into the left ventricle when the retrograde route is used, as in this and many other series, may result in failure to record a gradient, and in some patients this may have been the cause of discrepancy between the angiographic appearances of obstruction and the absence of a gradient. Furthermore, pockets in the left ventricle between the main ventricular cavity and the muscle mass might account for capricious gradients in some patients.

Right Heart Catheterization.—This was performed in 21 patients (Fig. 9), 13 of whom had a systolic pressure gradient between the right ventricle and pulmonary artery of more than 10 mm. Hg. Gradients usually lay between the body or apex of the right ventricle and the right ventricular outflow tract, rather than between the right ventricular outflow tract and the pulmonary valve (Fig. 10).

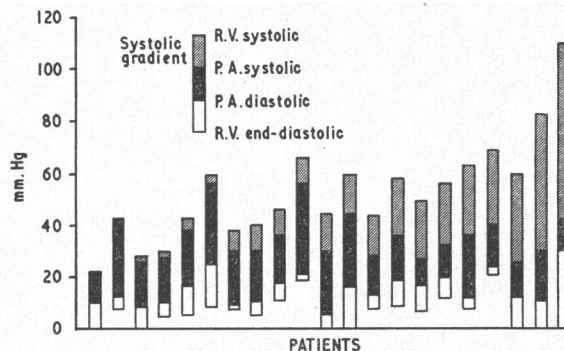


FIG. 9.—Data from right heart catheterization in 21 patients with hypertrophic obstructive cardiomyopathy.

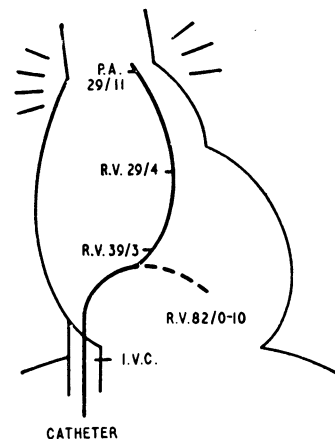


FIG. 10.—Diagram showing position of gradient in right ventricle between apex and outflow tract in a girl, aged 18, with hypertrophic obstructive cardiomyopathy. PA=pulmonary artery. RV=right ventricle. IVC=inferior vena cava.

The right ventricular end-diastolic pressure was moderately elevated, but less so than the left ventricular end-diastolic pressure (Fig. 9). Mean right atrial pressure was not remarkable, but prominent "a" waves transmitted to right ventricular pressure pulses were often seen, as in Fig. 11. The end-

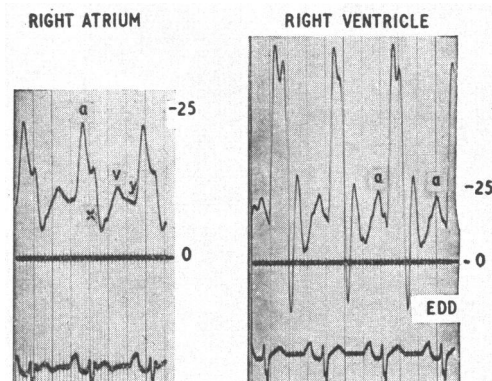


FIG. 11.—Right atrial and right ventricular pressure pulses in a patient with hypertrophic obstructive cardiomyopathy. The augmented pre-systolic (a) wave in the right atrial pulse is transmitted to the right ventricle. There is considerable right ventricular systolic hypertension, and the end-diastolic pressure is elevated. This, and the early diastolic dip (EDD) (though the latter is partly due to under-damping in the recording system), indicate resistance to ventricular filling.

diastolic hypertension and the early diastolic dip in this figure, though partly due to artifact, indicates abnormal resistance to ventricular filling.

Cardiac output (Fig. 12) in contrast with other forms of cardiomyopathy was high, indicating, in view of the high systolic ventricular pressures, that ventricular work was normal or even increased.

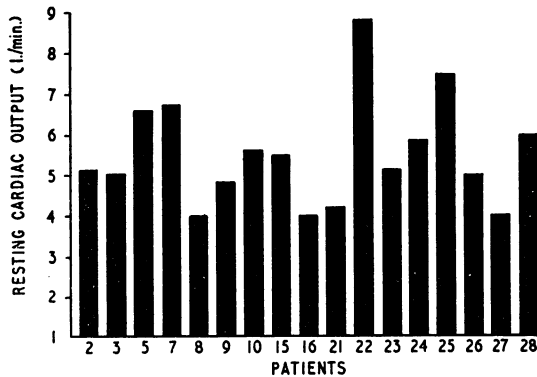


FIG. 12.—Cardiac output in hypertrophic obstructive cardiomyopathy.

Right Ventricular Angiocardiology.—In 20 patients this showed distortion of the right ventricle by the hypertrophied ventricular septum, which bulged into the cavity (Special Plate, Fig. III). Systolic constriction between body and outflow of the right ventricle was seen and often irregular masses of muscle also encroached on the right ventricular, as on the left ventricular, cavity. The tricuspid and pulmonary valves were normal.

Features of Condition

These haemodynamic and angiographic studies indicated two main features; massive hypertrophy of the ventricular muscle and disturbance of function. The hypertrophy was borne out by the electrocardiogram, which showed lone left ventricular hypertrophy or biventricular hypertrophy and enlargement of both atria (Fig. 13). The duration of systole corrected for heart rate (QT_c) was usually prolonged, also reflecting the considerable muscular hypertrophy (Hollister and Goodwin, 1963). A short PR interval suggesting premature ventricular excitation was found in three of our patients (Cohen *et al.*, 1964).

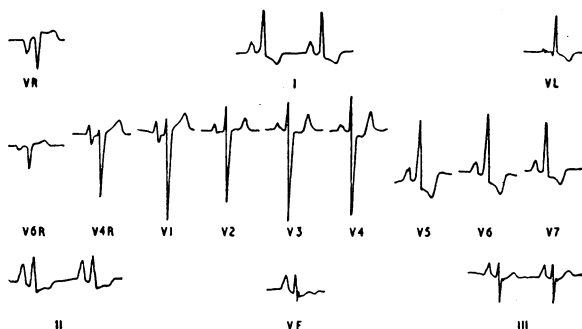


FIG. 13.—Electrocardiogram of a boy, aged 8, with hypertrophic obstructive cardiomyopathy showing prolonged duration of systole (QT_c 0.55/sec.). The tall R waves and inverted T waves in leads V_1 and V_6 , and the left axis deviation, indicate marked left ventricular hypertrophy.

Studies of the pathology of the condition bear out the presence of massive hypertrophy (Fig. 14) as has been found by Teare (1958), Hollman *et al.* (1960), Menges *et al.* (1961), Wigle *et al.*, (1962), and others. The hypertrophy of the ventricles is generalized, but the main enlargement involves the septum and accounts in part at least for the obstruction to outflow and inflow.

Histologically there is hypertrophy of the muscle fibres, and in some cases, but not all, the bundles appear unusually large and their arrangement bizarre. An excessive amount of fibrous tissue may be present.

Further knowledge regarding structure and function has been obtained from surgical exploration, and from the effects of certain drugs.

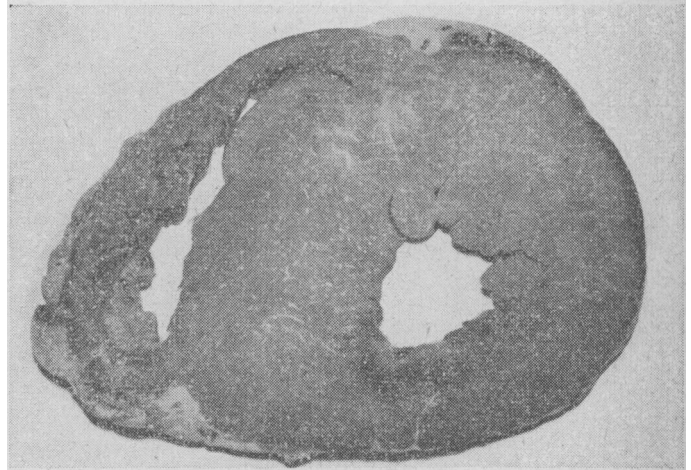


FIG. 14.—The heart in hypertrophic obstructive cardiomyopathy showing generalized hypertrophy and massive enlargement of the septum with patchy fibrosis.

Surgical Treatment

A number of attempts have been made to remove or reduce the obstruction to outflow by surgical means (Braunwald *et al.*, 1960; Goodwin *et al.*, 1960, 1961; Morrow and Brockenbrough, 1961; Kirklin and Ellis, 1961; Nordenström and Ovenfors, 1962; Wigle *et al.*, 1963).

Eleven patients in the present series were operated on by my surgical colleagues, Mr. W. P. Cleland and Mr. H. H. Bentall, using cardiopulmonary bypass directed by Dr. Denis Melrose. The outflow tract of the left ventricle was approached *via* the aorta during cardiopulmonary bypass. Variable degrees of obstruction to left ventricular outflow were found and gradients were extremely capricious. In some cases where these had been present at catheterization they were absent at thoracotomy, and occasionally gradients found at thoracotomy were not reduced by substantial muscle resection. In one patient a gradient was present at thoracotomy even though the subvalvar region showed no apparent localized obstruction, though diffuse hypertrophy was present. Functional obstruction may be absent in the arrested flaccid heart (Goodwin *et al.*, 1961; Nordenström and Ovenfors, 1962), but Braunwald *et al.* (1960) noted a contraction ring in the outflow tract of the left ventricle when the heart was kept beating by coronary perfusion.

In our patients as much tissue was removed as possible, though in some this was only a small amount. A deep incision was made into the outflow tract (ventriculomyotomy) and left bundle-branch block was produced in all but one patient. Three patients died during or after the operation, but the eight who survived have all been improved symptomatically. Full haemodynamic and angiographic follow-up studies are in progress and will be reported later.

In view of the small amount of tissue that was often removed, and the variability of the gradients, it seems likely that a functional disorder plays at least an appreciable part in the production of obstruction, and, therefore, of pressure gradients. In view of this, the incision of the ventricular muscle and perhaps the production of left bundle-branch block are probably crucial to a successful result. Wigle *et al.* (1963) recently reported a reduction in the pressure gradient following ventriculomyotomy, though left bundle-branch block was not produced in every

case. In hypertrophic obstructive cardiomyopathy the first beat after a ventricular ectopic beat has a higher systolic left ventricular pressure and outflow gradient, indicating that the more forcefully the ventricle contracts the more obstruction is produced (Brockenbrough *et al.*, 1961). It is thus worth noting that left bundle-branch block has been shown to reduce the force of left ventricular contraction and to prolong isometric contraction in a patient with aortic incompetence (Bourassa *et al.*, 1962), and might favour a reduction in gradient. It is not known whether the production of left bundle-branch block is purely incidental or of importance in relieving functional obstruction. In one patient with massive ventricular hypertrophy the surgeon reported that the obstructing mass of muscle felt stiff, inelastic, and abnormal.

Thus, surgical studies have confirmed the massive hypertrophy, revealed obstruction in some cases, and indicated the functional nature of the obstruction in many.

Essentially, this form of cardiomyopathy consists of massive hypertrophy and disturbance of blood flow. The latter abnormality takes the forms of obstruction to outflow and undue resistance to inflow. The resistance to inflow is due to inadequate yielding of ventricular muscle in diastole, which has been ascribed by Braunwald *et al.* (1960) and by Wigle *et al.* (1962) to loss of compliance of the grossly hypertrophied ventricular muscle. This seems a most reasonable explanation, but in our experience the elevation of left ventricular end-diastolic pressure has sometimes been out of proportion to the degree of hypertrophy, so that a fault in the behaviour of the muscle independent of hypertrophy might be a factor (Cohen *et al.*, 1964), though the rapidity of the isometric relaxation phase suggests that the ventricular muscle relaxes normally. Resistance to outflow is due both to massive muscle hypertrophy encroaching on the left ventricular outflow tract and also to an abnormality of function such as asynchronous contraction of various components of the left ventricular musculature.

Effects of Drugs on Ventricular Function

The variability of gradients has led Braunwald and Ebert (1962), Whalen *et al.* (1963), and Krasnow *et al.* (1963) to study the effects of inotropic drugs such as isoprenaline on the outflow tract gradient in patients with hypertrophic obstructive cardiomyopathy. Isoprenaline is a sympathomimetic drug with a pure inotropic action causing powerful myocardial contraction, tachycardia, and peripheral vasodilation. It has been shown to increase or produce an outflow tract gradient, the left ventricular systolic and end-diastolic pressures rising, and the systemic arterial or aortic pressure falling. When this occurred Braunwald and Ebert reported that the cardiac output fell or remained constant and the effective outflow orifice of the left ventricle diminished. Conversely, methoxamine, a pure peripheral arteriolar vasoconstrictor with no inotropic action, abolished the gradient in similar patients (Braunwald and Ebert, 1962). Furthermore, these workers showed that in patients with true aortic valve stenosis isoprenaline did not reduce the effective size of the orifice or increase left ventricular diastolic pressure. But the cardiac output rose, and so the gradient increased. The findings in hypertrophic obstructive cardiomyopathy, if unique to this disorder, indicate the importance of a functional element and confirm that stimulation of abnormally functioning muscle bundles may intensify or cause obstruction to ventricular outflow.

Our own studies have so far been limited, but we have confirmed the effect of isoprenaline in increasing or producing a gradient between left ventricle and aorta, though the left ventricular diastolic pressure did not rise in our patients.

Using a two-catheter technique (one catheter in the body of the right ventricle *via* the saphenous vein, and the other in the pulmonary artery or outflow pathway of the right ventricle *via* an antecubital vein) we have extended our observations to

the right side of the heart and shown that gradients between the body and outflow tract of the right ventricle may be increased or produced by isoprenaline as on the left side of the heart (Fig. 15).

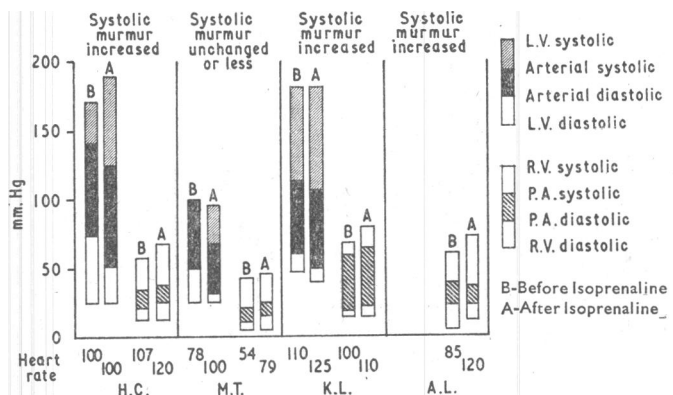


FIG. 15.—Isoprenaline studies in hypertrophic obstructive cardiomyopathy (2 μ g. injected through cardiac catheter). The right and left heart studies were made on different occasions. SM=systolic murmur.

We have confirmed that isoprenaline increases outflow obstruction while phenylephrine (a pure peripheral vasoconstrictor without any inotropic action) diminishes the murmur in association with a bradycardia. In one of the two patients on whom the drug was tried, ventricular alternans was abolished (Fig. 16).

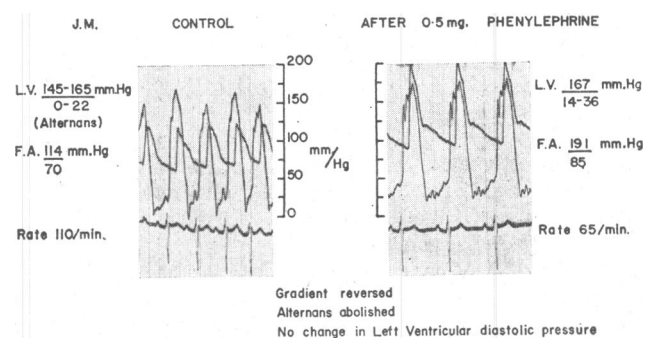


FIG. 16.—Left ventricular and femoral artery pressure pulses before and after phenylephrine was injected through the cardiac catheter in a patient with hypertrophic obstructive cardiomyopathy.

We have also studied the effect on the gradients and murmurs in hypertrophic obstructive cardiomyopathy of the beta-adrenergic-blocking agent "alderlin" (pronethalol, nethalide), which blocks the cardiac excitatory reactions to catecholamines, and sympathetic nerve stimulation (Black and Stephenson, 1962; Dornhorst and Robinson, 1962). The results have not been impressive, but my colleague, Dr. Pravin Shah, has shown that pronethalol will prevent an isoprenaline-induced gradient and tachycardia. The main effects of pronethalol might therefore be to suppress excessive inotropic action of endogenous catecholamines.

It has not been possible to estimate rapid changes in cardiac output in these studies, and it may well be that nethalide can reduce the gradient by causing a fall in cardiac output.

In addition, we have found that pronethalol given chronically as a therapeutic measure to three patients with hypertrophic obstructive cardiomyopathy caused dyspnoea in two, possibly as a result of inhibition of catecholamine action in the heart. But in one of them dramatic relief of exertional dyspnoea was attributable to nethalide.

Braunwald *et al.* (1962) have shown that digitalis has the same effect as isoprenaline in creating or increasing outflow tract gradients in hypertrophic obstructive cardiomyopathy, and is therefore presumably contraindicated in this condition, though

its action as a vagal stimulant might be expected to be beneficial in slowing the heart rate. My own experience, however, has been that digitalis, as in the normal heart, does not produce appreciable bradycardia in this condition, presumably because true heart failure is rare.

Unclassified Group

The six patients in this group showed features common to one or more of the other three groups, but did not clearly fall into any particular one. Gallop rhythm was common, and short ejection and mid-diastolic murmurs suggested that there might be an element of muscular hypertrophy or obstruction to ventricular outflow and inflow respectively.

Right atrial pressures were low, never exceeding 5 mm. Hg. Right ventricular systolic pressures were normal in three patients, slightly elevated in one, and markedly elevated in two. Like the hypertrophic obstructive group and unlike the congestive or constrictive groups, systolic gradients were found of 15 mm. Hg in one patient and 30 mm. Hg in another between right ventricle and pulmonary artery. Right ventricular diastolic pressures were always below 10 mm. Hg, resembling in this the congestive rather than the constrictive hypertrophic obstructive groups. Mean indirect left atrial pressures were normal in three and elevated in two patients (Fig. 17). The cardiac output tended to be higher than in either the constrictive or congestive groups.

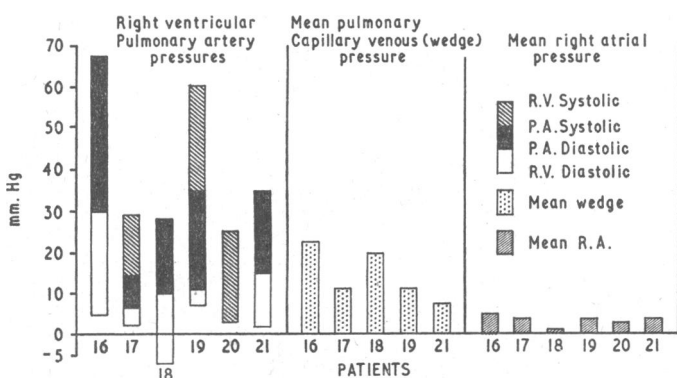


FIG. 17.—Haemodynamics in unclassified cardiomyopathy.

Radiology of the heart showed a rather globular contour, resembling the findings in the hypertrophic obstructive group rather than the other two groups, while angiocardigraphy revealed three main abnormalities. Firstly, there was little difference between systolic and diastolic size, suggesting poor contractility and impaired ventricular compliance; secondly, there was enlargement of both ventricles; and thirdly, irregular muscular hypertrophy and bulging of the ventricular septum into the cavity of the right ventricle was found. These abnormalities were not constant in all patients, suggesting that either the patients were in different stages of the same disorder, suffered from different aspects of the same disorder, or had different disorders.

Special Plate, Fig. V, shows enlargement of both ventricles and little difference in chamber size between systole and diastole in one patient. There was no pressure gradient between left ventricle and aorta, and both left and right atrial pressures were normal in this patient.

Special Plate, Fig. VI, shows considerable enlargement of the left ventricle and only slight variation between the cavity size

in systole and diastole. There was no pressure gradient between left ventricle and aorta, but in contrast to the previous patient the left atrial mean pressure was considerably raised, being 24 mm. Hg. The right atrial pressure was normal. In neither of these patients could the lack of change in cavity size during the cardiac cycle be attributed to poor contraction of the ventricles due to ectopic beats.

Special Plate, Fig. VII, shows an angiocardigram from a third patient in this group and indicates considerable variation in size of the left ventricular cavity between systole and diastole and also appreciable muscular hypertrophy of the left ventricle, without obvious obstruction to outflow, though some narrowing is seen below the aortic valve reminiscent of the hypertrophic obstructive group. No mitral incompetence can be seen and no ectopic beats occurred during the injection of the contrast medium. This patient had systemic hypertension (not found in other patients in the series). There was no gradient between the left ventricle and aorta, but the left ventricular diastolic pressure was raised, being 210/22/40 mm. Hg. The indirect left atrial pressure showed "a" and "v" waves of 21 mm. Hg, but the right atrial pressure was normal.

Electrocardiograms tended to show rather more striking left ventricular hypertrophy than in the first two groups, especially sharp T wave inversion in left precordial leads (Fig. 18).

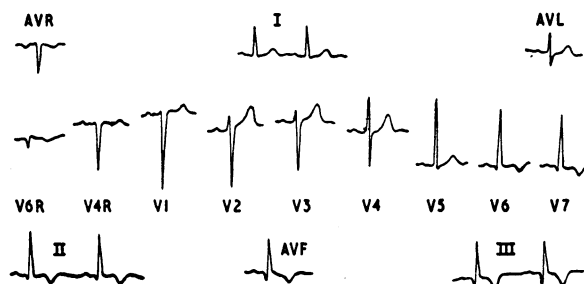


FIG. 18.—Patient aged 12. Electrocardiogram in unclassified primary cardiomyopathy showing sharp T wave inversion in left precordial leads with tall R waves. Similar changes are seen in leads II, III, and VF, reminiscent of posterior infarction.

Thus in this group features not seen in the congestive and constrictive groups were present. Muscular hypertrophy was striking, reduced myocardial excursion was found, and the presence of outflow gradients from the left ventricle was noteworthy, but as the patients in the first two groups were not studied by left heart catheterization no comparison on this point can be made. It seems unlikely, however, that the patients with congestive and constrictive cardiomyopathies did have systolic left ventricular outflow pressure gradients in view of the lack of other evidence of obstructive features.

Though angiograms in the patients in the unclassified group were not typical of hypertrophic obstructive cardiomyopathy, they nevertheless presented similar features, consisting of considerable muscular hypertrophy and restriction of diastolic ventricular size. It seems possible that these patients represent examples of hypertrophic obstructive cardiomyopathy in an early obstructive or pre-obstructive phase, but it is impossible to be certain. However, the existence of this unclassified group does indicate that myocardial function and structure in the cardiomyopathies is by no means uniform, and shows considerable variation. The presence of deep T wave inversion in left precordial leads of the electrocardiogram in the absence of clinical evidence of outflow tract obstruction favours a hypertrophic type.

[The conclusion of this article, with the list of references, will be published next week.]