Papers and Originals

Disorders of the Outflow Tract of the Left Ventricle*

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[WITH SPECIAL PLATE]

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The left ventricle has recently been elegantly described by Walmsley and Watson (1966). It is bounded above by the aortic valve, anteriorly and above by the membranous portion of the ventricular septum, and below by the muscular septum. Posteriorly above lies the anterior cusp of the mitral valve and, below, the chordae tendineae and the papillary muscles. Part of the membranous septum is in direct contact with the right atrium and close to the tricuspid valve (Special Plate, Fig. 1).

Many diseases may involve the outflow tract of the left ventricle and produce either a pressure or a volume load. In those which produce a volume load, dilatation of the cavity is due to the extra volume of blood regurgitated in diastole in aortic regurgitation, or entering the left ventricle as a result of a left-to-right shunt from an aortic-pulmonary communication such as a patent ductus arteriosus or from a ventricular septal defect. The increased ventricular volume necessitates an increased stroke volume, which is achieved by hypertrophy of the muscle.

Obstructive lesions such as aortic valve stenosis, discrete subaortic stenosis due to a muscular bar beneath the aortic valve, and diffuse hypertrophy of the septum in hypertrophic obstructive cardiomyopathy impose a pressure load on the left ventricle and stimulate great hypertrophy of the walls of the ventricle without increase in the size of the cavity.

The mitral valve apparatus is crucial in maintaining the integrity of the outflow tract, and thus it is not surprising that disorders of the mitral valve apparatus may be closely associated with disorders of the left ventricular outflow tract.

The left ventricle has been described by Rushmer (1961) as a cylindrical cavity with a conical apex. Contraction of the left ventricle involves reduction in the diameter of the chamber and elongation of the long axis which are achieved by two sets of muscles—the deep and superficial bulbo-muscles, which cause contraction of the long axis and shortening of the chamber, and the constrictor muscles, which cause reduction in the diameter of the cavity.

The left ventricle is ideally suited by its anatomy for sustaining high pressures against a heavy load, but when this load becomes unbearable hypertrophy develops as a compensatory mechanism. Linzbach (1960) and Grant *et al.* (1965) have introduced the concepts of concentric and of eccentric hypertrophy. When the ventricle is faced with a volume load, such as occurs in severe aortic regurgitation (each ejection being augmented by the regurgitation from the previous cycle), the cavity enlarges but the wall remains about the same thickness. An obstructive lesion such as aortic valve stenosis imposes a pressure load, which leads to concentric hypertrophy, the wall thickness increasing disproportionately to the size of the cavity, which remains small. Grant *et al.* (1965) have studied relative wall thickness in patients with obstruction to left ventricular outflow and those with a volume load due to regurgitation. The relative wall thickness was measured by dividing the actual thickness of the wall of the left ventricle by the mean radius of the cavity, the measurements being obtained angiographically. Fig. 1, from their paper, shows the great increase in relative wall thickness in obstructed ventricles as compared with normal subjects and those with regurgitation. Grant *et al.* (1965) have also shown that in obstruction with concentric hypertrophy stroke work can be augmented without an increase in end diastolic volume, but with a rise in end diastolic pressure.

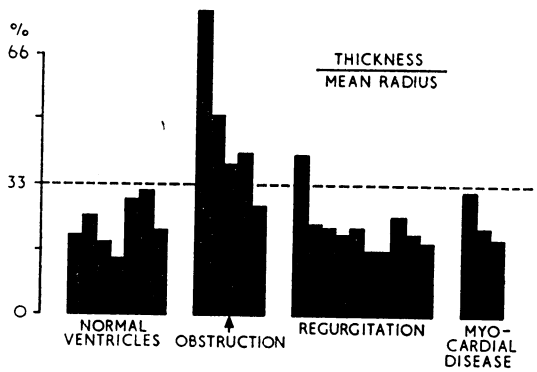

FIG. 1.—Relative wall-thickness (thickness of ventricular wall/mean radius of cavity) of normal left ventricle, obstructed left ventricle, volume-loaded left ventricle (regurgitation), and myocardial disease, showing marked increase in patients with obstruction to left ventricular outflow. Data obtained from angiocardiographic measurements. (Reproduced from Grant *et al.* (1965) by permission of the authors and the Editor of the *American Journal of Medicine*.)

When concentric and eccentric hypertrophy coexist there is an increase both in cavity volume and in wall thickness.

Mitral Regurgitation (Table 1)

Mitral regurgitation and papillary muscle abnormalities are common in disorders of the left ventricle. We have used the term "subvalvar mitral incompetence" when regurgitation is due to disease of papillary muscles or chordae with normal valve cusps (Raftery *et al.*, 1966). Subvalvar mitral regurgitation may occur in patients who have fixed or variable obstruction to outflow. In the absence of obstruction to outflow, lesions which distort, obliterate, or destroy the cavity of the left

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ventricle, or which damage the papillary muscles or chordae, may also produce mitral regurgitation. Valvar mitral regurgitation unassociated with outflow obstruction, as in rheumatic heart disease, also causes a volume load upon the left ventricle, but less so than aortic regurgitation. When the ventricle is subjected to a volume load alone, so that the cavity becomes large in systole and is not encroached upon, distorted, or obstructed, subvalvar mitral regurgitation is usually absent.

TABLE I.—*Disorders of the Left Ventricle. Papillary Muscle Abnormality with Subvalvar Mitral Regurgitation*

With fixed or variable obstruction to outflow:
- Hypertrophic obstructive cardiomyopathy
- Discrete subaortic stenosis
- "Anomalous insertion" of the anterior mitral cusp (Björk
- Aortic valve stenosis

Without obstruction to outflow:
- Papillary muscle infarction (ischaemic heart disease
- Infection (bacterial endocarditis)
- Infiltration (sarcoidosis)
- Distortion and other lesions:
  - Endomyocardial fibrosis
  - Endocardial fibroelastosis
  - Aneurysm of the mitral valve ring
  - Parachute mitral valve (single papillary muscle)

Lesions Causing a Volume Load

Ventricular Septal Defect with Aortic Regurgitation

Disorders of the left ventricular outflow tract which produce mainly a volume load consist of patent ductus, aortic valve regurgitation, ventricular septal defect, ventricular septal defect with aortic regurgitation, and fistulae from the sinus of Valsalva to the right side of the heart. The lesion which produces one of the most massive volume loads is severe aortic regurgitation. Patent ductus and ventricular septal defect separately produce smaller volume loads dependent upon the increased inflow to the left ventricle due to the left-to-right shunt.

When two causes for a volume load are combined, as in ventricular septal defect with aortic regurgitation, a very dangerous situation results. This is a rare combination of defects, but well recognized (Nellen *et al.*, 1959 ; Nadas *et al.*, 1964), and Dr. Hallidie-Smith has made a special study of 28 patients who have been seen in the Unit of Clinical Cardiology during the last seven years (Hallidie-Smith *et al.*, 1966). Twenty patients were treated surgically, an incidence which represents 9% of our total surgical series of 220 patients with ventricular septal defect. Sixteen were aged between 3 and 14 years, and the oldest was 35 years. All the patients who were operated on had severe aortic regurgitation, and four died. It is to be expected that in the future, with improved techniques of coronary perfusion and increased experience, the mortality will be significantly less.

A prolapsed, elongated, and possibly congenitally abnormal right coronary cusp was the cause of the aortic regurgitation in 14 patients. In three others there was deformity or perforation of the cusp, and three had an associated rupture of the sinus of Valsalva, two of these having a prolapsed cusp of the aortic valve. Thus bacterial endocarditis was not the cause of the aortic regurgitation, but apparently predisposed to it, for the incidence of bacterial endocarditis was much higher in this group than in our series of simple ventricular septal defects. The defect was usually large in size, being greater than 2 sq. cm./sq. m. body surface area in nine and greater than 1 sq. cm./sq. m. body surface area in only four patients. It was infracristal in 14 patients and supracristal in six. The incidence of supracristal defects was higher in this group (25%) than in the total group of surgically treated ventricular septal defects (4%).

Fig. 2 shows the way in which the aortic valve cusp tends partially to block the ventricular septal defect. This also tends to prevent the right ventricular systolic pressure equalling the left, and to create a gradient in systole between right ventricle and pulmonary artery. Two left-to-right shunts were seen—one from the aorta to the right ventricle in diastole, and the other from the left ventricle to the right ventricle in systole. Thus shunts were often large, the ratio of pulmonary to systemic flow being as much as three to one. Aortography (Special Plate, Fig. II) shows a dilated anterior sinus of Valsalva, considerable aortic regurgitation, and the passage of contrast medium into the right ventricle and thence into the pulmonary artery. The volume of the left ventricle is very large, consistent with two lesions both producing a volume load, and mitral regurgitation is absent.

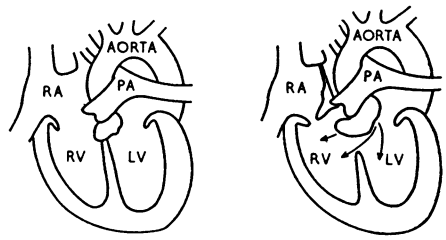

FIG. 2.—Diagram to show prolapse of the aortic cusp into the ventricular septal defect, partially blocking the defect and causing a systolic gradient between pulmonary artery and right ventricle. RA=Right atrium. RV=Right ventricle. LV=Left ventricle. PA=Pulmonary artery. The arrows denote the shunt from aorta into the right ventricle, and also the leak from aorta into the left ventricle.

Aortic regurgitation complicating ventricular septal defect is a serious and progressive lesion and heart failure is common. Marked left ventricular enlargement is usual, both clinically and radiologically, and the electrocardiogram reflects the increased load upon the left ventricle, showing inverted T waves in left precordial leads which do not occur in lone ventricular septal defect. We believe that the progressive nature of the disease and the tendency to bacterial endocarditis are indications for surgical treatment when aortic regurgitation supervenes in a patient with a ventricular septal defect.

Lesions Causing a Pressure Load with Fixed Obstruction

Lesions which produce a pressure load and concentric hypertrophy are aortic valve stenosis and discrete subvalvar stenosis consisting of a muscular or fibromuscular bar extending across the outflow tract beneath the aortic valve. Abnormal insertion of the anterior mitral cusp into the right coronary cusp of the aortic valve also tends to produce obstruction to left ventricular outflow and mitral regurgitation (Björk *et al.*, 1961).

Aortic Valvar Stenosis

Dr. Oakley has studied 40 young patients with congenital aortic valve stenosis, and has shown that not only can the diagnosis of the site of the obstruction be made convincingly at the bedside but the severity of the condition can also be assessed (Oakley and Hallidie-Smith, 1967). The characteristic auscultatory sign is an ejection murmur at the aortic area and at the cardiac apex. The murmur is preceded by a click (Vogel and Blount, 1965) which is the result of doming of the abnormal valve into the aorta at the beginning of ventricular ejection (Raftery, 1965). In mild cases the murmur is short and the peak intensity lies in the first half of systole. But in severe or extreme cases the murmur is long and the peak lies in the middle or in the second half of systole. Aortic valve closure may be delayed owing to prolongation of left ventricular ejection (Fig. 3). The systolic pressure gradient across the aortic valve can be related to the interval between the click and the peak of the murmur expressed as a percentage of the ejection time of the left ventricle. The later the peak of the murmur the higher the gradient, and, after successful operation, as the gradient becomes less so the murmur tends to reach its peak

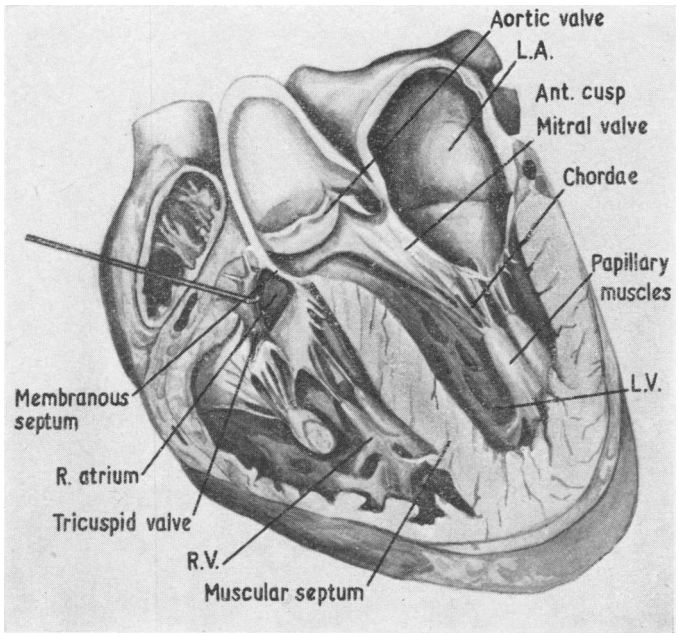

FIG. I.—Drawing of section through the heart showing all four chambers and aorta. L.V.=Left ventricle. R.V.=Right ventricle.

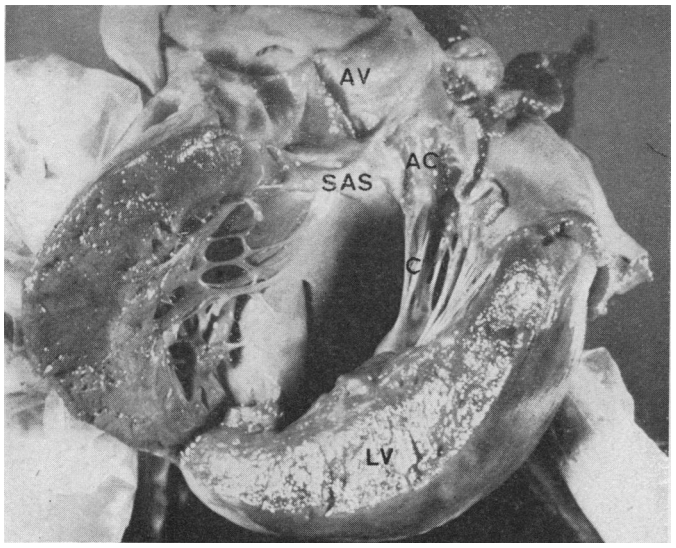

FIG. III.—Necropsy specimen of a heart with aortic valvar stenosis and with discrete subvalvar aortic stenosis to show hypertrophy of the left ventricular wall, the fibromuscular stenotic bar (SAS) beneath the aortic valve (AV) and the close relation to the mitral chordae (C), papillary muscles, and anterior mitral valve cusp (AC). (Reproduced by courtesy of Dr. E. Olsen.)

FIG. II.—Ventricular septal defect and aortic regurgitation. Aortogram (lateral projection), A, showing passage of contrast medium from aorta (Ao) into left ventricle (LV), and B, from the ventricular septal defect into the right ventricle (RV) and pulmonary artery (PA). The anterior sinus of Valsalva (SV) is dilated, the ventricular volume is considerably increased, and there is no mitral regurgitation (A).

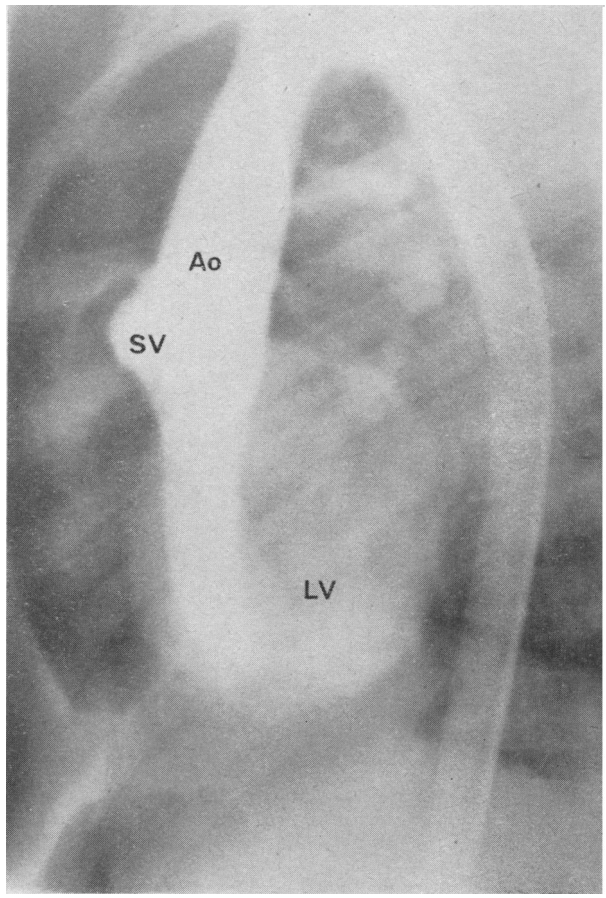

FIG. IIA

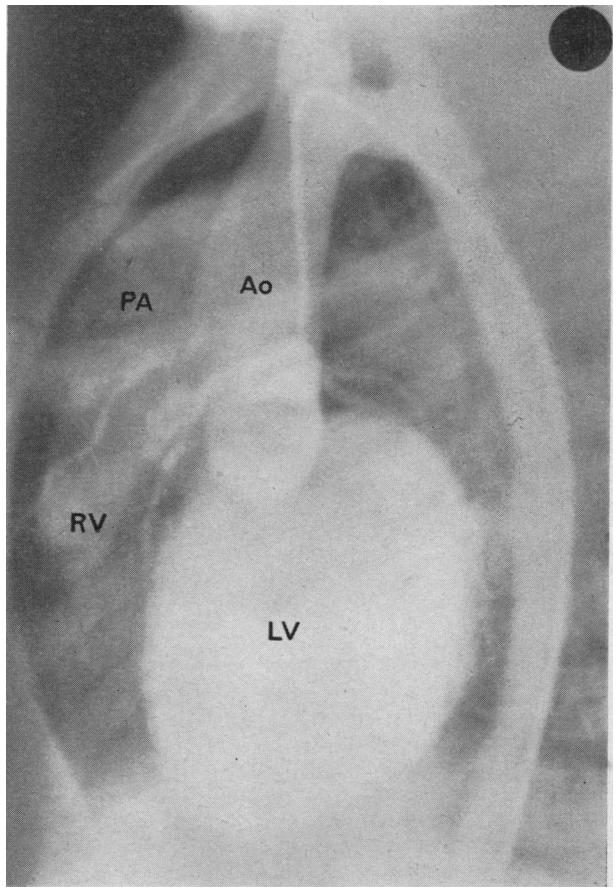

FIG. IIB

J. F. GOODWIN: DISORDERS OF THE OUTFLOW TRACT OF THE LEFT VENTRICLE

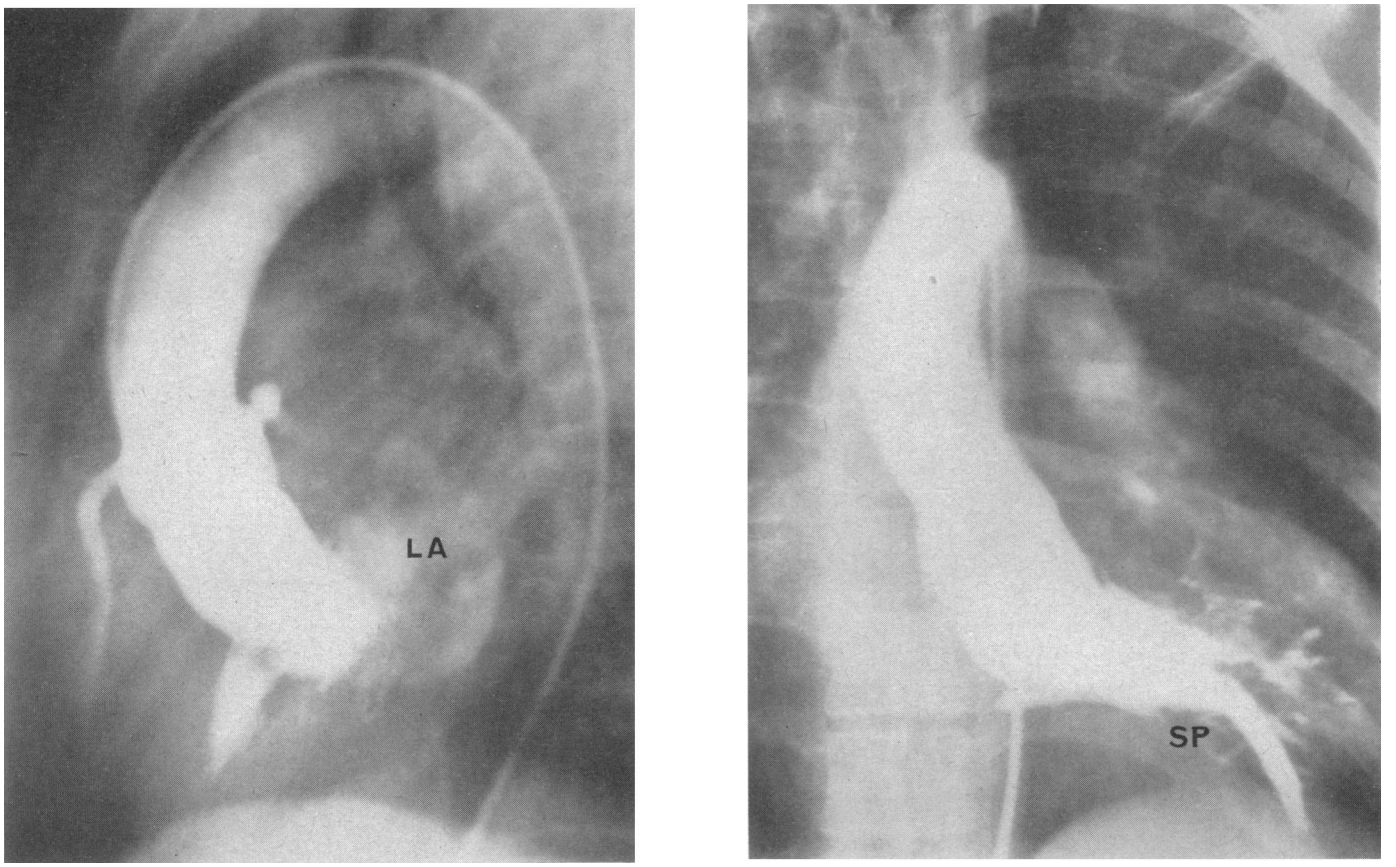

FIG. IV.—Left ventricular angiocardiogram (systolic phase), lateral projection (left) and frontal projection (right), in hypertrophic obstructive cardiomyopathy, showing normal aorta and aortic valve, large coronary arteries, and narrowing of ventricular cavity with intrusion of large muscle masses into the cavity, especially in the region of the septum and papillary muscles (SP). Contrast medium is seen in the left atrium (LA) owing to mitral regurgitation.

B. CORRIN AND J. C. MEADOWS: SKELETAL METASTASES FROM CEREBELLAR MEDULLOBLASTOMA

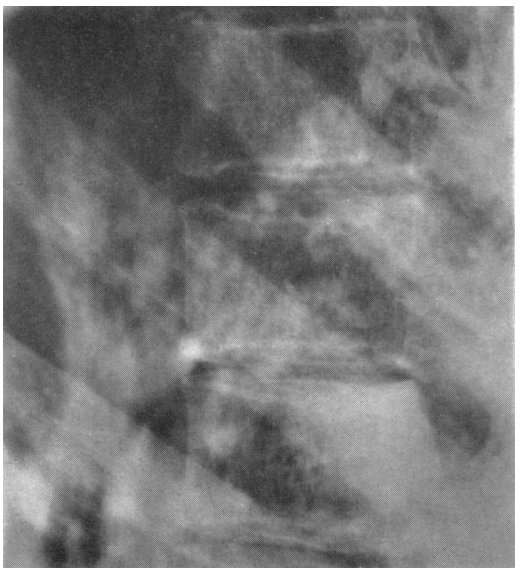

FIG. 1

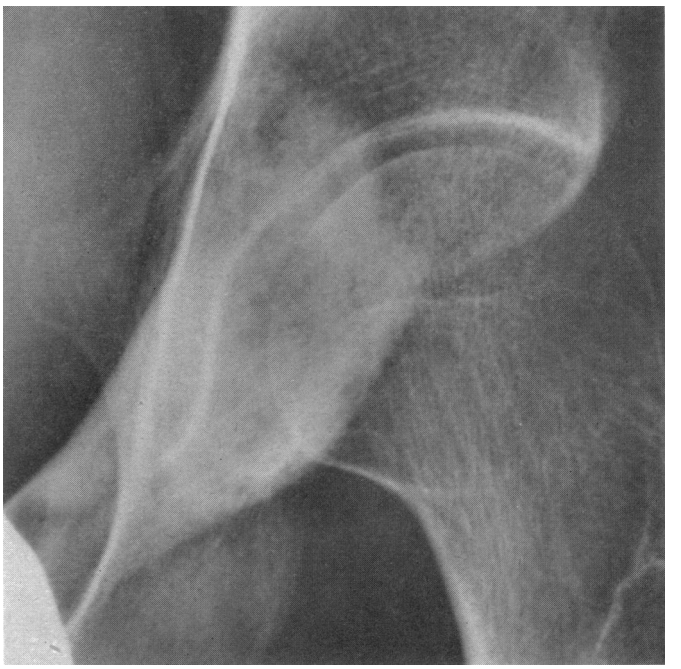

FIG. 2

FIGS. 1 and 2.—Osteosclerotic metastases in a vertebral body and acetabulum.

earlier in systole. The timing of the maximum intensity of the murmur is a better guide to severity than the length or intensity of the murmur, which can be both long and loud with mild obstruction.

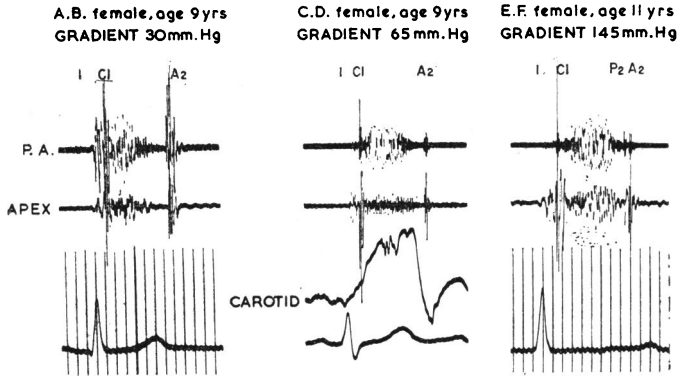

FIG. 3.—Phonocardiograms from three patients with congenital valvar aortic stenosis showing the early systolic click (Cl), the maximum intensity of the murmur occurring in the latter half of the systole; and delayed aortic valve closure (A2) in the most severe case (E. F.). 1=First heart sound. P_2=Pulmonary valve closure. Gradient=systolic pressure difference between left ventricle and aorta. Electrocardiogram (and in Case C. D. carotid pulse tracing) are below. (Reproduced from Oakley and Hallidie-Smith (1967) by permission of the authors and the Editor of the *British Heart Journal*.)

Aortography shows doming of the valve and an eccentric narrow orifice and jet of non-opacified blood. Aortic regurgitation is absent or slight in the majority of these patients.

Subvalvar mitral regurgitation has been described in congenital aortic valvar stenosis due to infarction of the papillary muscle resulting from relative ischaemia (Moller *et al.*, 1966).

Discrete Subaortic Stenosis

Dr. Oakley has also studied 21 patients with discrete subvalvar aortic stenosis, and has shown that the physical signs on auscultation differ strikingly from valvar stenosis (Oakley and Hallidie-Smith, 1967). In subvalvar stenosis there is no click because the aortic valve is normal, but owing to the presence of the obstructive bar immediately below the valve the valve fails to close properly, and thus aortic closure is very soft or inaudible and is followed by an early diastolic murmur (Fig. 4). Indeed, the auscultatory findings are very similar to older patients with heavily calcified aortic valvar stenosis in whom the aortic valve neither opens nor closes fully. Left ventricular angiography reveals a normal aortic valve and a localized obstruction below it. Mitral regurgitation is common, but its exact frequency is difficult to assess as it requires retrograde left ventricular angiography for its demonstration and this was not performed in all 21 patients. The occurrence of mitral regurgitation is not surprising when the close relation of the subaortic bar to the mitral chordae tendineae and papillary muscles is noted (Special Plate, Fig. III).

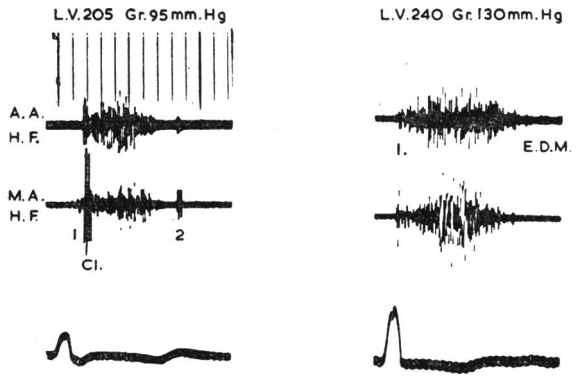

FIG. 4.—Phonocardiogram in congenital valvar stenosis (left) and discrete subvalvar stenosis (right). In subvalvar stenosis aortic valve closure is not seen and there is an early diastolic murmur of aortic regurgitation. There is no click. LV=Left ventricle. Gr=Systolic pressure difference between left ventricle and aorta. 1=First heart sound. 2=Second heart sound. Cl=Click. EDM=Early (aortic) diastolic murmur. (Reproduced by courtesy of Dr. C. M. Oakley.)

Lesions Causing Pressure Load Due to Variable Obstruction

Hypertrophic Obstructive Cardiomyopathy

Hypertrophic obstructive cardiomyopathy was probably first discovered by Schmincke in 1907, but was first described in this country by Brock (1957), who, operating on a patient with aortic stenosis, found a normal aortic valve and massive muscular hypertrophy of the septum obstructing outflow. The condition was later described by Teare (1958), who demonstrated the massive asymmetrical hypertrophy of the septum, and also hypertrophy of the free wall of the left ventricle. Conventional histological studies show massive hypertrophy of muscle fibres, which are arranged in a bizarre fashion, and variable amounts of fibrosis.

The condition was described clinically by Morrow and Braunwald (1959) as functional aortic stenosis, and by us (Goodwin *et al.*, 1960) as obstructive cardiomyopathy. Braunwald *et al.* (1960) introduced the term "idiopathic hypertrophic subaortic stenosis" by which title the disease is now known in North America. We (Cohen *et al.*, 1964) later introduced the word hypertrophy into our definition, and the condition is now known as hypertrophic obstructive cardiomyopathy in this country. We now have experience of over 80 patients with this disorder.

The clinical picture is now well-known. There is commonly a family history (Paré *et al.*, 1961). The symptoms are usually those of syncope and angina, while sudden death is not uncommon. Dyspnoea is often present, but is usually mild or moderate and is very rarely severe. The most important physical signs consist of a jerky arterial pulse, a double cardiac impulse due to a palpable atrial beat, and an ejection murmur of late onset heard best at the left sternal edge and towards the apex. Early ventricular ejection is more rapid than normal, and 70% of the left ventricular contents are ejected by the powerful strongly acting hypertrophied chamber (Ross *et al.*, 1966), when there is a systolic gradient in the ventricle. Most of the ventricular contents are ejected in the first half of systole (Fig. 5). Angina is probably due to increased demands of the hypertrophied left ventricle, for Lewis (1966), working in Brink's laboratory at Stellenbosch University, has shown that, though coronary blood flow is increased, anaerobic metabolism occurs.

The cause of the murmur is usually thought to be obstruction to outflow, but this is not always the case, as shown in Fig. 6 by a microphone catheter in the left ventricle indicating that the

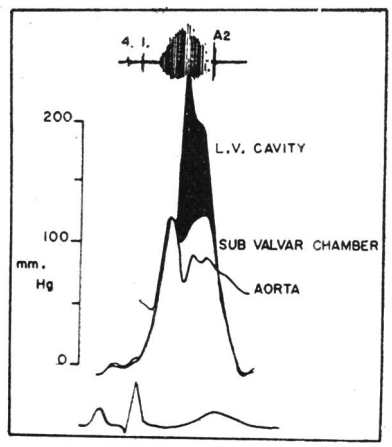

FIG. 5.—Simultaneous left ventricular and aortic pressure pulses, electrocardiogram (below), and phonocardiogram (above) in hypertrophic obstructive cardiomyopathy to show fourth heart sound (4), late systolic murmur, and pressure gradient. Note the notch on the ascending limit of the left ventricular pressure pulse at onset of the gradient. L.V.=Left ventricle. A_2=Aortic valve closure. (Reproduced by courtesy of Dr. C. M. Oakley.)

murmur is maximal in the outflow tract at a time when there is no pressure gradient. The murmur, however, increases in intensity when a pressure gradient is induced. There are probably several explanations for its cause, particularly turbulence within the hypertrophied strongly, rapidly contracting ventricle ; outflow tract obstruction, either variable as in most cases or fixed as in those with extreme muscular hypertrophy ; and, finally, mitral regurgitation, which may account for a loud murmur in the absence of much evidence of obstruction.

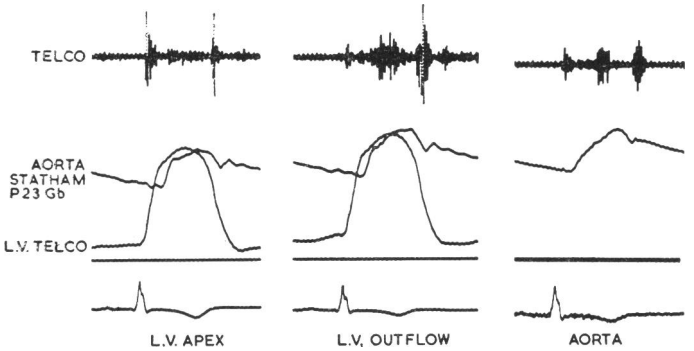

FIG. 6.—Intraventricular phonocardiogram (Telco) and left ventricular and aortic pressure pulses in the apex of the left ventricle (L.V.), the outflow tract, and the aorta in hypertrophic cardiomyopathy. Note the maximum intensity of the murmur in the outflow tract in the absence of any intraventricular gradient.

Left ventricular angiocardiography reveals a normal aorta and aortic valve, and large coronary arteries. The left ventricle is narrowed by enormous masses of muscle, and the cavity may be slit-like, with sometimes a portion apparently isolated from the rest of the ventricle. The main obstructing masses appear to lie in the region of the septum and the papillary muscles (Special Plate, Fig. IV). Mitral regurgitation is seen in many cases and may possibly be present in some degree in all. When hypertrophy of the septum is massive, the septum may encroach on the right ventricle and produce gradients in systole in the right ventricular cavity, and between right ventricle and pulmonary artery. Signs suggesting impairment of inflow are also seen. Enormous hypertrophy of the muscle may be present, but is not always associated with obstruction, and in some cases hypertrophy appears to be the lone or dominant lesion. While many cases show considerable outflow tract gradients, some show none, but in the majority the left ventricle enddiastolic pressure is raised. This is due to gross concentric hypertrophy and poor compliance of the ventricle, so that the left atrial pressure rises, and this accounts for breathlessness and possibly for difficulty in filling the ventricle (Cohen *et al.*, 1964).

Dr. Colin Grant (1967), when working with Professor Steiner and with my unit, studied the endsystolic volume, ejection fraction, and relative wall thickness measured angiographically in seven of our patients with hypertrophic obstructive cardiomyopathy. The endsystolic volume was smaller than normal in all but one, and the ejection fraction was greater in all, as was the relative wall thickness (Table II). These findings confirm the great hypertrophy and complete emptying of the ventricle.

TABLE II.—*Hypertrophic Obstructive Cardiomyopathy. Endsystolic Volume (E.S.V.), Ejected Fraction (E.F.), and Relative Wall Thickness of L.V. (Grant, 1967). Modified from Grant et al.* (1965)

Patient Case No.	E.S.V. (ml./sq.m.)	E.F.	Relative Wall Thickness % (*Wall Thickness* Mean Cavity Radius)	Pressure Gradient (mm. Hg)
1	15	0·88	59	20
2	20	0·82	41	160
3	22	0·83	55	70
4	31	0·69	33	40
5	33	0·73	41	59
6	38	0·78	44	39
7	42	0·61	48	37
Mean ..	29	0·76	46	
Normal ..	36	0·64	27	
S.D.	12	0·10	8	

The electrocardiogram has been intensively studied in 55 patients in our series by my colleague Dr. Levin. He has noted the frequency of right and left ventricular hypertrophy, of combined atrial hypertrophy, and of Q waves in septal leads, previously described by Wigle *et al.* (1963). Many of our patients have a short P–R interval, suggesting some degree of conduction abnormality (Fig. 7), but by contrast true bundle-branch block, atrioventricular block, and atrial fibrillation are extremely rare. The tendency to a short P–R interval may suggest some form of accelerated conduction between atria and ventricles.

Left axis deviation is due to interference with the parietal branches of the left bundle resulting from fibrosis of the septum, which is also the cause of the Q waves seen in central chest leads.

The variability of the outflow tract gradients is well known. In Fig. 8 gradients at two examinations have been compared, and, while in five patients they are in good agreement, in the other four they are widely at variance. Gradients may vary as a result of emotion or exercise, and the increase in gradient after an ectopic beat described by Brockenbrough *et al.* (1961) is now well known. The arterial pressure is lower and the left ventricular pressure higher in the pause which follows a ventricular ectopic beat.

There are a number of determinants of left ventricular systolic pressure gradients, notably changes in ventricular volume and in contraction (Fig. 9). When the ventricular volume is reduced the walls of the ventricle tend to approximate and the gradient increases (Braunwald *et al.*, 1964). Hypovolaemia, hypotension, peripheral vasodilatation, as with amyl nitrite, all have this effect. Dr. Oakley has shown (Shah *et al.*,

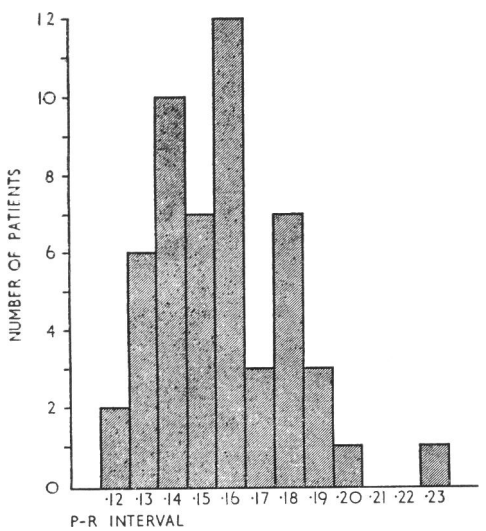

FIG. 7

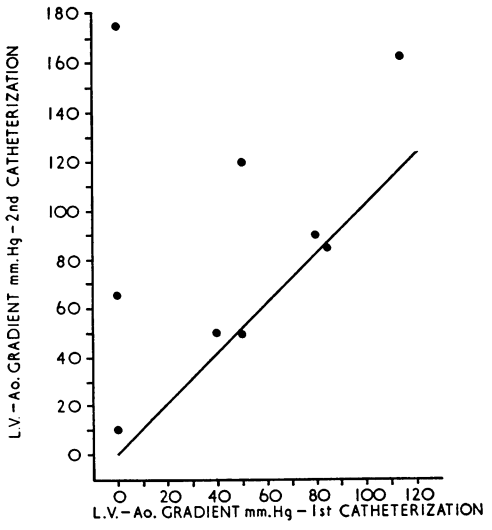

FIG. 8

FIG. 7.—Histogram showing P–R interval in hypertrophic obstructive cardiomyopathy. (Levin, 1965.)
FIG. 8.—Systolic gradients compared at two different examinations in the same patients to show variations in hypertrophic obstructive cardiomyopathy. (Levin, 1965.)

1965a) that rapid venesection will increase the gradient and subsequent transfusion will reduce it. Conversely, measures which increase the volume of the heart will push the hypertrophied walls apart and reduce the gradient. This may happen in hypervolaemia, in hypertension, and in peripheral vasoconstriction. Braunwald *et al.* (1964) have shown that methoxamine and phenylephrine, which produce peripheral vasoconstriction without any central cardiac action, are most effective in abolishing the gradient and in reducing the intensity of the murmur, and we have confirmed this (Goodwin *et al.*, 1964). Congestive heart failure may have the same effect, but is rare in obstructive cardiomyopathy, and when it occurs often follows the onset of atrial fibrillation and a fall in cardiac output. In pregnancy, which is associated with increased circulatory volume and salt retention, the signs of obstruction may also diminish, and we have seen this in four out of five patients.

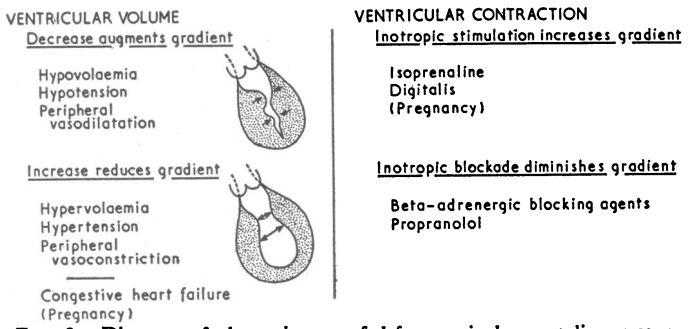

FIG. 9.—Diagram of determinants of left ventricular systolic pressure gradients in hypertrophic obstructive cardiomyopathy showing the way in which volume changes may alter the size of the left ventricular cavity and change the gradient.

Substances which augment or produce increased ventricular contraction, such as inotropic agents, digitalis, and isoprenaline, tend to increase or produce a gradient (Braunwald *et al.*, 1964). Inotropic blockade with beta-adrenergic blocking agents will diminish the gradient but will not influence gradients produced by changes in cardiac volume (Shah *et al.*, 1956b). Beta-adrenergic blockade in our experience is useful in diminishing gradients produced acutely, or in preventing the development of gradients, and is therefore likely to be valuable in the prevention of gradients during effort and under emotional stimulation in patients with this disease (Goodwin et al., 1964). We are now using the beta-adrenergic blocking agent propranolol for long-term treatment (Cherian *et al.*, 1966).

The detailed pathology of the outflow tract of the left ventricle has been studied by my colleague Professor Everson Pearse, who has examined the specimens removed from patients who have been treated by surgical methods. He has confirmed the enormous muscle hypertrophy, and shown wide, short, grossly hypertrophied muscle fibres. Electron microscopy shows not only the grossly hypertrophied fibres but an intense mitochondriosis, the mitochondria themselves being abnormal. Though neither of these features is specific to hypertrophic obstructive cardiomyopathy, Everson Pearse has also shown excessive amounts of noradrenaline in the outflow tract of these patients. This finding is apparently unique, and does not occur in patients with cardiac muscle hypertrophy from other causes (Everson Pearse, 1964).

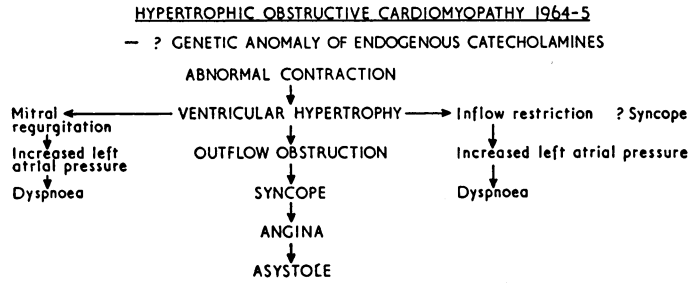

FIG. 10.—Scheme showing the role previously assigned to outflow obstruction in the genesis of symptoms and sudden death.

We have postulated (Goodwin, 1964) a genetic anomaly of endogenous catecholamines as the cause of this disease, leading to abnormal contraction, ventricular hypertrophy, outflow obstruction, syncope, and asystole. Until recently we considered obstruction to play the main part in the disease, though realizing that mitral regurgitation and inflow difficulties were also present (Fig. 10).

Criley *et al.* (1965) have drawn attention to the presence of artifactual systolic gradients in the left ventricle due to obliteration and isolation of areas of the cavity which trap the indwelling catheter. While such artificial gradients due to cavity obliteration undoubtedly occur, the presence of true outflow obstruction seems undoubted in view of the demonstration by Ross *et al.* (1966) of obstruction during systolic flow, 70% of the systolic volume being ejected during a period of gradient. Fig. 11, for which I am indebted to Dr. E. Braunwald, shows how a catheter (A) in the apex of the left ventricle can record a false gradient by cavity obliteration, while a catheter (B) in the outflow tract below the mitral valve records a true obstruction. The presence of bands and bars in the outflow tract at operation and a high systolic pressure zone in the outflow tract of the left ventricle also bear witness to the presence of true outflow obstruction under certain circumstances. In addition relief of obstruction can occur after division and/or resection of the obstructing area of outflow tract. Ross *et al.* (1966) believe that isometric pressure development and early ventricular ejection proceed more rapidly than normal, and that approximately 30% of the forward stroke volume is ejected while there is no significant pressure gradient. This early phase of systole is responsible for the sharp upstroke of the arterial pressure pulse. Then the hypertrophied septum approaches the anterior surface of the closed mitral valve and the interventricular pressure at all points in the cavity below this site begins to exceed that in the outflow tract. The pressure gradient from the body of the ventricle to the outflow tract then increases progressively as further narrowing of this region occurs.

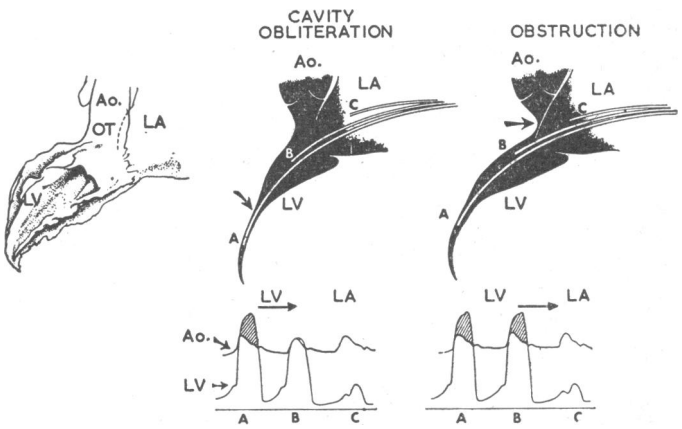

FIG. 11.—Cavity obliteration and true obstruction in hypertrophic obstructive cardiomyopathy. Catheter A in the apex of the left ventricle records a false gradient due to cavity obliteration, while catheter B lying in the outflow tract below the mitral valve records true obstruction. (Reproduced from Ross *et al.*, *Circulation*, 1966, **34**, 558, by kind permission of the authors, the Editor of *Circulation*, and the American Heart Association Inc.

Cavity obliteration can probably occur in any hypertrophied heart if the catheter is inserted deeply into the ventricular cavity, and has been produced in normal dogs (Morrow *et al.*, 1965), but I am personally convinced from Braunwald's work and our own experience that true obstruction occurs also in hypertrophic obstructive cardiomyopathy. However, the absence of significant obstruction in many cases, and the occurrence of sudden death in patients in our series without any evidence of outflow obstruction, have directed attention towards other aspects of the disorder, notably to the mitral regurgitation which is often present.

Relation of Subvalvar Mitral Regurgitation and the Papillary Muscles to Hypertrophic Obstructive Cardiomyopathy

Following the clinical appreciation that certain patients with chronic subvalvar mitral regurgitation had signs indistinguishable from hypertrophic obstructive cardiomyopathy, the clinical and haemodynamic features of four types of mitral regurgitation were studied.

Table III compares these four types of mitral regurgitation, the valvar rheumatic type, the acute subvalvar type due to papillary muscle infarction or chordal rupture, chronic subvalvar mitral regurgitation, and hypertrophic obstructive cardiomyopathy.

TABLE III.—*Cardinal Features in Different Types of Mitral Incompetence*

	With Volume Load		Without Volume Load	
	Rheumatic Mitral Regurgitation	Acute Subvalvar Mitral Regurgitation (Nonrheumatic)	Subacute Mitral Regurgitation (? H.O.C.M.)	Mild or Early H.O.C.M.
Onset of symptoms	Gradual	Sudden	Absent or gradual	Absent or gradual
Pulmonary oedema	0	+	0	0
Jerky arterial pulse	+	+	+	+
Systolic murmur	Pan. Apex	Ejection. Apex and base	Late. Ejection. Apex and base	Late. Ejection. Apex and base
Added sounds	Early diastolic. 3rd	Early diastolic. 3rd	Presystolic 4th (6 patients)	Presystolic 4th (5 patients)

H.O.C.M. = Hypertrophic obstructive cardiomyopathy.

In rheumatic valvar mitral regurgitation there is a volume load on the left ventricle, obstruction is absent, *systolic* volume is increased, there is a pansystolic murmur and third heart sound, and an early climbing "v" wave in the left atrial pressure trace. The same features are present in acute subvalvar regurgitation, except that the murmur is often ejection in type and conducted to the aortic area, as described by Burch *et al.* (1963) and by us (Raftery *et al.*, 1966), and the "v" wave in the atrial pulse is later.

By contrast, in chronic subvalvular regurgitation and in hypertrophic obstructive cardiomyopathy there is no volume load on the left ventricle, the *systolic* volume is reduced, and obstruction is often present. The murmur is ejection in type, and there is a fourth sound, with a large "a" wave in the left atrial pressure pulse, indicating hypertrophy of that chamber.

We (Oakley *et al.*, 1967) have studied six patients with chronic subvalvar mitral regurgitation and compared them with five patients with proved hypertrophic obstructive cardiomyopathy, and have shown that in respect of clinical signs, response of the murmur to drugs, and angiographic appearances they are identical.

In rheumatic mitral regurgitation, when the ventricle is subjected to a volume load, the administration of amyl nitrite by reducing the peripheral resistance diminishes the regurgitation, whereas phenylephrine by adding to the after-load on the ventricle tends to increase the regurgitation. But in chronic subvalvar regurgitation and in hypertrophic obstructive cardiomyopathy the situation is different. Amyl nitrite, by diminishing the systolic volume of the ventricle, increases the murmur. Phenylephrine by increasing the after-load, and thus the systolic ventricular volume, decreases the murmur.

Left ventricular cineangiocardiograms in moderately severe hypertrophic obstructive cardiomyopathy and in acute subvalvar mitral regurgitation are closely similar. Considerable mitral incompetence is associated with a tell-tale filling defect in the region of the septum and papillary muscles similar in site and type to that seen in severe hypertrophic obstructive cardiomyopathy.

Studies of ventricular volume by my colleague Dr. Maurice Raphael, using Arvidsson's (1961) angiographic method, has shown interesting differences between groups of patients (Fig. 12). The residual fraction represents the amount of emptying of the ventricle in systole, a residual fraction of 1.0 indicating virtually no emptying, and of 0.1 almost complete emptying. Patients with normal left ventricular function are shown on the left. Those with rheumatic mitral disease and with acute subvalvar mitral regurgitation who had a volume load acting on the ventricle have a higher residual fraction than normal. The largest residual volumes are found in congestive cardiomyopathy, where hypertrophy is but slight and ventricular dilatation considerable. In hypertrophic obstructive cardiomyopathy the residual fraction is small, reflecting the almost complete emptying which occurs, and in two patients with chronic subvalvar mitral regurgitation the residual fraction was within the lower range of hypertrophic obstructive cardiomyopathy.

An illustration reproduced from Tandler's (1923) textbook of a normal heart in systole, shows the crucial position of the papillary muscle (Fig. 13). It is easy to see how hypertrophy of the septum and papillary muscles could cause obliteration and encroachment on the cavity with isolation of more distal portions.

It is our current view that papillary muscle disorder plays an important part in the genesis of hypertrophic obstructive cardiomyopathy. Disease of these muscles may perhaps be the initiating lesion. In the normal ventricle, the papillary muscles tense and seal the mitral valve cusps in apposition during the

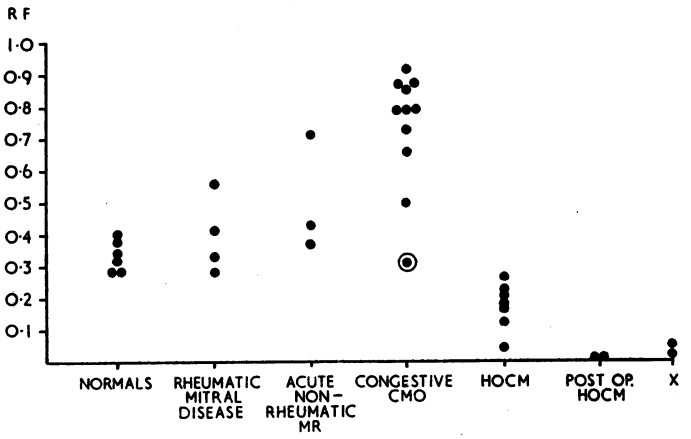

FIG. 12.—Residual fraction (RF) of left ventricular ejection measured angiocardiographically in a group of patients with normal left ventricles, and volume-loaded left ventricles, and with hypertrophic obstructive cardiomyopathy. The difference in residual fraction between rheumatic mitral regurgitation (MR), chronic subvalvar regurgitation, and hypertrophic obstructive cardiomyopathy is well seen. X represeats two patients with chronic subvalvar mitral regurgitation who have the smallest residual fraction. (See text.) (Reproduced by courtesy of Dr. C. H. Oakley and Dr. M. Raphael.)

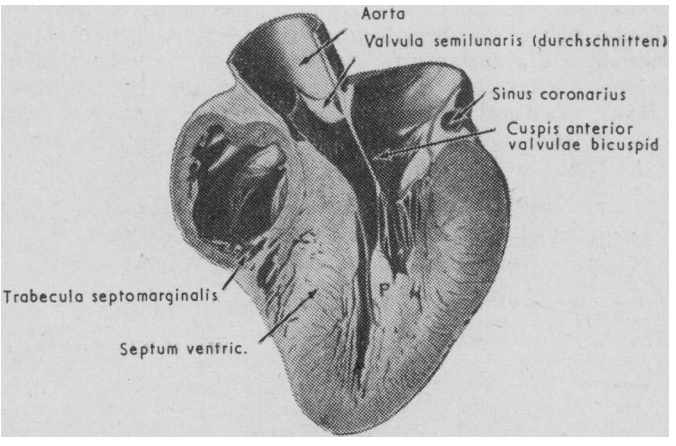

FIG. 13.—The normal heart in systole, showing relation of the papillary muscles (P) to the septum, and the narrow left ventricular cavity. Reproduced from Tandler (1926).

phase of isovolumetric contraction. During ejection the cavity size is reduced by the constrictor muscles and shortening of the long axis by the spiral muscles occurs. Full or nearly full emptying is achieved without mitral regurgitation (Rushmer, 1961). In hypertrophic obstructive cardiomyopathy premature contraction of the body of the ventricle or late contraction of the papillary muscles could cause outflow obstruction because the papillary muscles are out of place and bulge towards the hypertrophied septum. This anomaly might be followed by a vicious circle of concentric hypertrophy, further mitral regurgitation, and further outflow obstruction. The sudden decompression of the left ventricle by the onset of mitral regurgitation would tend to favour further obstruction by reducing the volume of the ventricular cavity (Fig. 14).

This postulate of papillary muscle disease as the initiating factor leaves still to be explained the presence of the fully developed disease in infants (Neufeld *et al.*, 1960 ; Daoud *et al.*, 1961), the presence of noradrenaline in the outflow tract of the left ventricle, and the development of a condition indistinguishable from hypertrophic obstructive cardiomyopathy in a few patients who have another cause for left ventricular outflow tract obstruction. The presence of excessive noradrenaline in the papillary muscles has yet to be demonstrated.

Brock (1957) originally thought that systemic hypertension might be the cause in some patients, and we have seen two patients with discrete subaortic stenosis who developed a syndrome indistinguishable on all counts from hypertrophic obstructive cardiomyopathy, and also a patient with aortic valve stenosis with clear features of hypertrophic obstructive cardiomyopathy. It may be that under certain circumstances the syndrome of hypertrophic obstructive cardiomyopathy can develop in response to other causes of left ventricular outflow obstruction and left ventricular disease, but I believe firmly that, for example, discrete subaortic stenosis and hypertrophic obstructive cardiomyopathy are different diseases, though sometimes they may be very difficult to distinguish, and the former may perhaps give rise to the latter.

Fig. 15 suggests consideration of the concept of primary and secondary hypertrophic obstructive cardiomyopathy ; secondary hypertrophic obstructive cardiomyopathy possibly resulting from discrete subaortic stenosis, from valvar aortic stenosis, or even from systemic hypertension. The contribution of increased circulating catecholamines is under study, and it is certain that the full story of hypertrophic obstructive cardiomyopathy has yet to be told.

Conclusions

Lesions of the left ventricular outflow tract lead either to a volume overload, producing eccentric hypertrophy, with a large cavity, or to a pressure overload with concentric hypertrophy, with thick walls, a small cavity, and increase in relative wall thickness.

An example of an extreme volume load is the combination of *ventricular septal defect and aortic regurgitation.* These lesions together impose a severe strain on the left ventricle. Aortic regurgitation is due to a prolapsed right coronary cusp in most cases, is progressive, leads to congestive heart failure, and predisposes to bacterial infection.

Discrete subvalvar aortic stenosis and *congenital valvar aortic stenosis* in children are easily distinguishable at the bedside. Both may be associated with mitral regurgitation, both impose a pressure load, and heart failure occurs late and only in severe cases. Sudden death may occur, perhaps from difficulty in ventricular filling.

Hypertrophic obstructive cardiomyopathy is associated with great concentric hypertrophy, with rapid ejection, and with filling difficulties. True outflow obstruction undoubtedly occurs, and is increased by reducing ventricular volume and by inotropic intervention, and relieved by increasing ventricular volume and by aninotropic intervention. The presence of excessive amounts of noradrenaline in the outflow tract of the left ventricle suggests that this may be an important factor in the disease. Mitral regurgitation is frequent. Early ventricular contraction and relatively late contraction of the papillary muscles may be important factors in the genesis of the disease, leading to mitral regurgitation, which would rapidly decompress the left ventricle. This rapid decompression could cause hypertrophy of the papillary muscles, followed by obstruction, further hypertrophy, and finally the complete syndrome. It is possible, therefore, that hypertrophic obstructive cardiomyopathy is primarily a disease of the papillary muscles associated with abnormal catecholamine function. But hypertrophic obstructive cardiomyopathy perhaps also occurs as a secondary phenomenon resulting from a fixed form of outflow tract obstruction, or from systemic hypertension.

Finally, it is clear that mitral regurgitation of the subvalvar type is common in obstructive disorders of the left ventricular outflow tract and that the anterior mitral cusp and papillary muscles are of crucial importance for the satisfactory function of the left ventricle.

Summary

The anatomy of the outflow tract of the left ventricle is briefly described, with special reference to the critical position of the anterior cusp of the mitral valve and the mitral subvalvar apparatus. Lesions which affect the outflow tract are divided into those which produce a volume load (eccentric hypertrophy), as in aortic regurgitation, and those which produce a pressure load (concentric hypertrophy), as in aortic stenosis. The syndrome of ventricular septal defect with aortic regurgitation is described to illustrate the effects of a severe volume load. Aortic valvar stenosis, discrete subvalvar stenosis, and hypertrophic obstructive cardiomyopathy are discussed in relation to their haemodynamic effects on the left ventricle and to their clinical features. The frequent association of subvalvar mitral regurgitation due to involvement of the papillary muscles in these conditions is emphasized. It is suggested that hypertrophic obstructive cardiomyopathy may result from asynchrony of

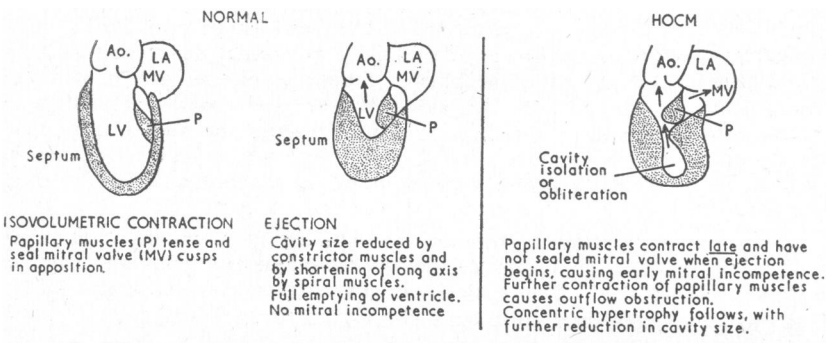

FIG. 14.—Diagrammatic representation of possible abnormal papillary muscle function in hypertrophic obstructive cardiomyopathy (see text). Ao=Aorta. LA=Left atrium. LV=Left ventricle.

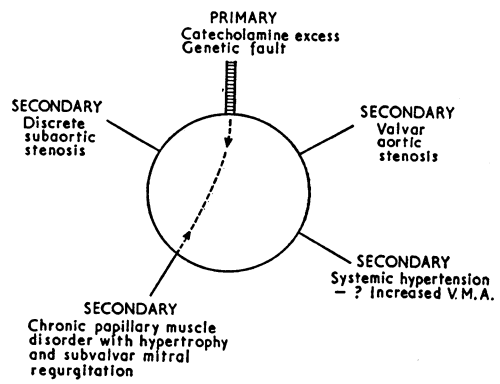

FIG. 15.—Diagram to show possible causes of primary and secondary hypertrophic obstructive cardiomyopathy (see text).

contraction between the body of the left ventricle and the papillary muscles, which leads to mitral regurgitation, rapid decompression of the left ventricle, and concentric hypertrophy. The importance of outflow tract obstruction and the possible contribution of excessive catecholamines within the heart in producing an abnormally powerful and rapid contraction of the left ventricle are debated.

It is concluded that while lesions which produce eccentric hypertrophy do not usually involve the papillary muscles or cause subvalvar mitral regurgitation, disorders which cause obstruction to outflow and which are associated with concentric hypertrophy and with reduction in the size of the cavity in systole are often associated with papillary muscle disorder and thus with mitral regurgitation.

I should like particularly to acknowledge the debt I owe to Professor Robert Steiner, Mr. William Cleland, and Professor Hugh Bentall. Much of the work described was performed in the Unit of Clinical Cardiology by Dr. C. M. Oakley, Dr. K. A. Hallidie-Smith, and Dr. E. B. Raftery. I also acknowledge the important work of Dr. Arthur Hollman in our earlier studies.

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Effect of Prostaglandin E_1 on Platelet Behaviour in Vitro and in Vivo

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Prostaglandins were first isolated by Goldblatt (1933) and von Euler (1934) from human seminal plasma and sheep seminal vesicles, and have since been found in other tissues (Bergström, 1965). One member of the group, prostaglandin E_1 (PGE_1), was shown to have very powerful vasodepressor activity, and in view of the close parallelism between the vasoactivity of compounds and their ability to affect platelet behaviour (Born *et al.*, 1965; Hampton *et al.*, 1967) it seemed likely that PGE_1 would be found to inhibit platelet aggregation.

Kloeze (1966) showed that in very low concentration PGE_1 could inhibit adenosine diphosphate (A.D.P.)-induced aggregation of rat, pig, and human platelets, and A.D.P.-induced glass adhesiveness of rat platelets. We report here some further effects of PGE_1 on aggregation induced by other agents, on glass adhesiveness in a whole-blood system, on the electrokinetic changes which A.D.P. and noradrenaline induce in platelets, and on the production of platelet thrombi in injured arteries in the rabbit.

Methods

Prostaglandin Solutions.—PGE_1 was dissolved in 96% ethanol to produce a stock solution of 100 μg./ml., which was stored at −20° C. The dilutions required for the various experiments were made by adding aliquots of the stock solution to normal saline.

Blood samples were taken into siliconized glass syringes from the antecubital veins of healthy volunteers or from hospital patients without acute illnesses or vascular disease. Then 9-ml. aliquots were transferred to siliconized centrifuge tubes containing 1 ml. of 3.8% trisodium citrate and gently mixed.

Platelet-to-glass adhesiveness in whole blood was measured by a modification of the Payling Wright (1941) technique (Emmons *et al.*, 1965a), and to assess the effect of PGE_1 0.1 ml. of normal saline or of PGE_1 in normal saline was added to 1.9 ml. of whole blood. Duplicate platelet counts were performed by the method of Brecher and Cronkite (1950) before and after rotating the 2-ml. samples in conical glass flasks for 40 minutes, and the fall in platelet count during rotation of the samples was expressed as a percentage of the initial count.

Platelet aggregation was studied by a modification of the Born (1962) optical density technique (Emmons and Mitchell, 1965). The optical density of platelet-rich plasma falls as aggregates form and rises again if they disperse. The fall

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