The frontiers of cardiomyopathy

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SUMMARY The history of cardiomyopathies over the past three decades is briefly surveyed and the definition of cardiomyopathy as "heart muscle disease of unknown cause" is reaffirmed. The recent slight modification of the classification based on disorders of structure and function into hypertrophic dilated (congestive) and restrictive/obliterative cardiomyopathy is underlined.

The hypothesis that hypertrophic cardiomyopathy results from abnormal catecholamine function in the developing heart is reviewed and supported. The concept of "obstruction" in hypertrophic cardiomyopathy is critically reviewed and challenged on the basis that true obstruction to outflow from the left ventricle is not present and that the pressure gradients often recorded are the result of elimination of the cavity of the ventricle as a result of powerful contraction of extensively hypertrophied muscle. The importance of impaired diastolic function with general and regional abnormalities of relaxation of a very complex nature is stressed. The natural history of hypertrophic cardiomyopathy is reviewed and the high incidence of sudden death confirmed in a personal series of over 250 patients studied over two decades. A relation between ventricular arrhythmia and sudden death has been noted. Studies of antiarrhythmic therapy disclosed that, while neither beta adrenergic blocking agents nor calcium blocking agents such as verapamil control arrhythmias studied by ambulatory tape monitoring, amiodarone is highly effective. It remains to be seen whether amiodarone will reduce the incidence of sudden death, the mechanism of which is discussed in the light of causes other than arrhythmia such as impairment of ventricular filling and reduction in left ventricular volume. A tentative scheme of treatment is suggested based on control of symptoms with beta adrenergic blocking agents and management of arrhythmias with amiodarone. The aetiologies of dilated congestive cardiomyopathy remain obscure. The possible place of virus infection leading to a disorder of cellular immunity is stressed.

Endomyocardial fibrosis as the leading cause of restrictive/obliterative cardiomyopathy is briefly described and the similarities in pathology and haemodynamics between endomyocardial fibrosis of the tropics and Loeffler's eosinophilic endomyocardial fibrosis are stressed. Evidence that the immature eosinophils found in patients with hyper eosinophilic syndrome and endomyocardial disease can damage the endocardium is reviewed.

Finally, the involvement of cardiomyopathies in many fields of general internal medicine is stressed and it is suggested that no longer are the cardiomyopathies rare or curious diseases but relatively common disorders which are of interest to medical scientists in many fields and no longer the sole problem of the cardiologist.

Historical aspects

Three decades ago the frontiers of cardiomyopathy were ill defined and nebulous because no working definition or classification had been suggested and

delineation was imprecise. The cardiomyopathies were often confused with myocarditis, a term used widely in a variety of pathological and clinical contexts without clarity of expression: myocarditis was sometimes equated with cardiomyopathy, sometimes with a specific inflammatory disorder.¹ In the United States of America, Mattingly, Burch, and Proctor Harvey were selecting and studying cases in the 1950's while in 1957 Brigden published his St Cyres

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lecture on "uncommon myocardial diseases; the non coronary cardiomyopathies".² Brigden pointed out the diversity of the disorder and the difficulty of classification and was among the first to use the term "cardiomyopathy". Not surprisingly he regarded the cardiomyopathies as rare disorders which indeed they seemed to be at that time.

My interest was kindled by Brigden's approach and in 1961 with colleagues Gordon, Hollman, and Bishop our first paper was published defining cardiomyopathy and attempting a classification.³ The definition was clumsy but was slightly modified in a subsequent paper on cardiac function in primary myocardial disorders as follows: "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".⁴ At this time it was suggested that the term "primary myocardial disorder" should be used to describe those cardiomyopathies that were not the result of diseases in other parts of the heart, or elsewhere in the body; subsequently, in conjunction with Dr Celia Oakley, the definition of cardiomyopathy was simplified to "a disorder of cardiac muscle of unknown cause" while myocardial disorders that were part of a general systemic disease were termed "rare specific heart muscle diseases".⁵ Thus automatically any condition of which the cause or pathological process could be defined clearly was excluded from the definition of cardiomyopathy. This concept has not always been readily accepted but has received approval from the joint task force of the World Health Organisation and International Society and Federation of Cardiology on the definition and classification of cardiomyopathies.⁶

The concept of a classification based upon the disorders of structure and function was introduced in 1964⁴ when it was suggested that cardiomyopathies might present clinically in one of three ways; as congestive, constrictive, or obstructive types, respectively.

Subsequent work has shown that these types are distinct entities that do not merge from one into the other. It has also been recognised that the "obstructive" type is notable mainly for massive ventricular hypertrophy and impaired diastolic function. The definition was revised to "hypertrophic obstructive cardiomyopathy"⁷ when it was realised that massive hypertrophy was a cardinal feature of the disease. At this time it was generally agreed that obstruction to outflow of the left ventricle was an important feature of the condition, though it had been recognised that in some patients no such obstruction existed. The importance of obstruction was first questioned by Criley *et al.* in 1965⁸ and by our group in 1971. We noted that as the disease became more severe the signs

of obstruction tended to disappear.⁹ Since then, the evidence for true obstruction has become significantly less.

In addition to the hypertrophic, congestive, and constrictive types, a new group was introduced, that of obliterative cardiomyopathy, to indicate the effects of endomyocardial fibrosis in obliterating the cavity of the ventricle.^{10 11}

Recently, three further changes have been made in the classification in the light of increasing knowledge. First, the word "obstructive" has been omitted from the definition of hypertrophic obstructive cardiomyopathy, and this type has come to be known simply as hypertrophic cardiomyopathy.¹²⁻¹⁴ Second, the importance of ventricular dilatation in congestive cardiomyopathy has been recognised by the use of the word "dilated" in the definition. The term "congestive", which was introduced in 1961³ at a time when diagnosis was seldom made before the development of florid congestive heart failure, is now felt to be inappropriate, especially as cases can now be recognised before overt congestive failure has occurred. Nevertheless, it is useful to retain the word "congestive" because it has become authenticated by frequent usage and its omission could cause confusion.

Third, the restrictive and obliterative types have been combined into one group (restrictive/obliterative) because it is known that the obliteration is merely a late stage of the restrictive type (when resulting from endomyocardial fibrosis) and a separate obliterative group is therefore not warranted⁶ (Fig. 1).

It is important to emphasise the terminology used. *Elimination* refers to disappearance of the ventricular cavity by compression and apposition of its walls. *Obstruction* refers to organic mechanical hindrance to ventricular outflow. *Resistance to filling* refers to hindrance to ventricular filling caused by a stiff, irregularly relaxing, poorly compliant, hypertrophied ventricle. *Restriction to filling* refers to organic interference resulting from endomyocardial disease of the ventricle with endocardial fibrosis and thrombosis.

Despite the modifications inseparable from the growth of understanding, the classification of the cardiomyopathies has basically stood the test of time over two decades. Since any classification is necessarily incomplete and acts as a bridge between complete ignorance and total understanding in any biological system, further modification and changes are likely to occur as knowledge advances over the next two decades, and new discussions may widen the frontiers of cardiomyopathy further.

Fig. 1 shows the major characteristics of hypertrophic, congestive (dilated), and restrictive/obliterative types.

In the hypertrophic type, which is familial, there is

Fig. 1 Types of cardiomyopathy. (Modified from *The heart*, 4th ed. J W Hurst, R B Logue, R C Schlant, N K Wenger, editors. McGraw-Hill, New York. By permission of the editors and publishers.)

massive muscle hypertrophy, concentration of hypertrophy in the septum, powerful systolic function, but abnormal relaxation. I now believe that obstruction in hypertrophic cardiomyopathy does not occur in a true haemodynamic and mechanical sense though gradients do develop and are important.

By contrast, the congestive dilated type has dilatation of the ventricular cavities and very poor pump function as its major characteristics. It is manifest by heart failure of unknown origin. It is now known that restrictive and obliterative cardiomyopathies are different stages of the same disease, restrictive cardiomyopathy usually being caused by endomyocardial fibrosis either of the tropical variety or of the temperate zone variety with eosinophilia, as described by Loeffler in 1936.¹⁵

It is the objective of this paper to indicate the direction of new advances and knowledge and to show how cardiomyopathies extend into the realms of many branches of medicine. No attempt will be made to be

comprehensive or exhaustive but rather to be stimulating and provocative.

Indeterminate diseases

There are other disorders that cannot easily be classified but perhaps may be regarded as cardiomyopathy. These are: the arrhythmic syndrome in which heart failure may be produced by multiple repetitive arrhythmias which, if relieved, can be followed by improvement in heart failure; various disorders localised to the conducting tissue; prolapsing mitral valve syndrome; the long QT syndrome; and angina with "normal" coronary arteries. It is not known whether this last syndrome is the result of a primary metabolic disorder or of a vascular problem but there are undoubtedly many subsets within this definition, in some of which the chest pain is not cardiac in origin.

Hypertrophic cardiomyopathy

The causation of hypertrophic cardiomyopathy is unknown but there are various clues which suggest that there may be a link between catecholamines, endocrine disorders, and hypertrophic cardiomyopathy. Experimental data show that the administration of nerve growth factor can cause hypertrophy, gradients, and myocardial fibre disarray in dogs, which also have an increased amount of catecholamines in the base of the heart. The condition so produced is irreversible. Witzke and Kaye¹⁶ suggested that there might be abnormal receptors in the heart. Laks *et al.*¹⁷ and Blaufuss *et al.*¹⁸ have shown that noradrenaline in subhypertensive doses causes hypertrophic cardiomyopathy in dogs. In the clinical field adrenergic stimulation increases gradients and reduces diastolic compliance in the left ventricle, while beta adrenergic blockade reverses these effects.¹⁹ There is an association between disorders of catecholamines and neural crest tissue, such as neurofibromatosis, pheochromocytoma, and lentiginosis.²⁰⁻²² Friedreich's ataxia^{23 24} is also associated with a hypertrophic type of cardiomyopathy and some evidence of autonomic disorder.^{23 24} In addition, systemic hypertension is present in around 10% of patients with hypertrophic cardiomyopathy. The finding of extensive noradrenosis in the outflow tract of the left ventricle in hypertrophic cardiomyopathy by Everson Pearse²⁵ has not been confirmed.

There is additional evidence of an endocrine character. Reversible hypertrophic cardiomyopathy has been noted in the infants of diabetic mothers.²⁶ Triiodothyroacetic acid (TRIAC) given to pregnant rats caused myofibrillar disarray in the heart of the fetus but not of the mother.²⁷ There is an association between hyperthyroidism and hypertrophic cardiomyopathy.^{28 29} Hyperinsulinism and hypoglycaemia may be associated with hypertrophic cardiomyopathy and increased catecholamine excretion. Experimental fetal hyperinsulinism causes selective

organ enlargement including the heart and it has been suggested there may be insulin receptors in the heart.³⁰ Hyperinsulinism and cardiac hypertrophy occur in the Leprechaun syndrome.³¹ A relation between hypercalcaemia and catecholamines has been proposed by McFarland *et al.*³²

I have, therefore, speculated whether hypertrophic cardiomyopathy may be a genetically determined disorder of handling of catecholamines by the developing fetal heart.^{1 11} Ferrans *et al.*³³ noted the similarity of the abnormal myofibrillar arrangements to the normal appearances in primitive hearts such as the salamander, while Manasek³⁴ had previously noted that the normal myofibrillar alignment depends on the stresses of contraction and relaxation of the developing heart. Abnormal alignment resulting from developmental error might affect relaxation and contraction.

Perloff³⁵ has summarised the evidence for the pathogenesis of hypertrophic cardiomyopathy based on this catecholamine hypothesis. He agreed that hypertrophic cardiomyopathy might well have its origin in utero. This would harmonise with my suggestions^{1 11} that hypertrophic cardiomyopathy might be the result of abnormal responses of developing heart muscle to circulating catecholamines. Perloff added the interesting suggestion that there may be a failure of the normal regression of disproportionate septal thickness and myocardial fibre disarray in fetal life because of faulty interaction between noradrenaline and myocardial receptor sites.

Work on catecholamines and hypertrophic cardiomyopathy in man has been scanty but Dargie *et al.* (to be published) at the Royal Postgraduate Medical School have shown that plasma noradrenaline increased in the lying and standing positions during the cold pressor test and isometric handgrip, as compared with controls (Fig. 2). But these studies of peripheral catecholamine levels give little idea of cardiac catecholamine status. Further work is planned to investigate the catecholamine function of the heart.

Table 1 Causes of sudden death in hypertrophic cardiomyopathy

Cause	Mechanism	Reason	Frequency	Prevention
(1) Arrhythmia	(a) Ventricular tachycardia (increased automaticity; local re-entry)	Myofibrillar disarray and fibrosis	Common	Amiodarone
	(b) Pre-excitation	Abnormal connections between atrium and ventricle bypassing A/V node	Rare	Amiodarone
(2) Haemodynamic	Reduction in left ventricular volume with apposition of ventricular wall and septum and loss of effective output (gradients variable); violent contraction of hypertrophic left ventricle	Resistance to filling of stiff incompliant left ventricle; tachycardia limiting time available for filling; loss of atrial contraction; powerful rapid contraction of left ventricle	Uncertain	Avoid: vasodilatation; hypotension; hypovolaemia and avoid: undue tachycardia (SR or AF); positive inotropic drugs unless AF demands digitalis

Fig. 2 Plasma noradrenaline levels in patients with hypertrophic cardiomyopathy (HOCM) and in control subjects in lying and standing positions and after isometric handgrip and cold pressor stimulation. There is a significant increase in catecholamine levels in the cardiomyopathy patients. (Reproduced by permission of Dr Henry Dargie.)

WHAT IS OBSTRUCTION?

I have stated¹⁴ that true obstruction is a myth. It has been assumed, and is still accepted in many quarters, that true obstruction of blood flow from the left ventricle is an important feature of hypertrophic cardiomyopathy. It is true that pressure gradients in systole are commonly, though not invariably, present and that they are of importance. They do not, however, constitute genuine haemodynamic obstruction to outflow in the accepted sense as, for example, occurs in severe valvar aortic stenosis. The variability of the gradient; the lack of correlation between gradients and prognosis, symptoms, or progression of the disease; the discharge of all the contents of the left ventricle in the first half of systole and the tendency for gradients to disappear as the disease advances,⁹ together with a tendency for more widespread ventricular involvement to be unassociated with a gradient^{33,36} all support this contention. Furthermore, gradients can be produced in any heart by powerful inotropic stimulation or acute ventricular hypovolaemia.⁸ These views are supported by the elegant work of Murgu *et al.*³⁷ who measured high velocity flow and pressure in the left ventricle and aorta. These workers were unable to show any evidence of true obstruction to outflow from the left ventricle. Ejection was completed earlier than in normal subjects and was independent of gradients. They concluded that hyper-

trophy and abnormal ventricular compliance play the dominant roles in hypertrophic cardiomyopathy.

Angiocardiology shows almost complete or complete elimination of the apex and body of the left ventricle in systole in many cases and demonstrates the apposition of the mitral valve to the septum caused by the powerful contraction and the reduction in ventricular volume. The abnormal angulated shape of the left ventricle with massive papillary muscles of the mitral valve and massive hypertrophy of the septum and free wall is associated with greatly reduced left ventricular volume in systole (Fig. 3). The cavity is virtually squeezed out of existence by the fierce contractile action of the increased muscle mass. Indeed the cavity of the left ventricle is neither *obstructed* nor *obliterated*, but rather is *virtually eliminated*.

Systolic anterior movement of the mitral valve apparatus and mid-systolic closure of the aortic valve are present when gradients are found.³⁸ It is the papillary muscles rather than the cusp of the mitral valve, however, that meet the hypertrophied septum.³⁹ The apex of the left ventricle is eliminated by the powerfully contracting hypertrophied muscle mass (Fig. 4, Fig. 5).

Gradients, however, are important and should not be dismissed. They are diagnostically valuable; they warn that powerful inotropic agents, manoeuvres, or drugs that reduce ventricular volume can be dangerous; the presence of persistent gradients warns of possible associated fixed outflow tract obstruction requiring operation; and finally septal resection in selected patients can produce symptomatic relief though it does not improve prognosis.

I do not support the view of Gilbert *et al.*⁴⁰ that there are two types of patients with hypertrophic cardiomyopathy: those with obstruction (persistent or latent) and those without, with significant differences in function and prognosis. The presence or absence of gradients appears to be largely coincidental and not an indication of the basic and important underlying abnormalities of the disease.

DIASTOLIC FAULTS

The work of Webb Peplow *et al.*¹⁹ in our laboratory and later at St Thomas's Hospital⁴¹ showed that beta adrenergic blocking agents administered acutely produced an increase in left ventricular volume and a fall in left ventricular diastolic pressure, suggesting an improvement in diastolic function. It was suggested¹¹ that catecholamine stimulation produced a fall in volume with an increase in diastolic pressure and beta blockade produced the reverse.

The rates of filling and relaxation of the left ventricle were studied by our group in collaboration with Dr Derek Gibson of the Brompton Hospital. Using angiocardigraphic⁴² and echocardiographic techni-

Fig. 3 (a) Left ventricular angiogram in hypertrophic cardiomyopathy showing elimination of the mid-portion and apex of the left ventricular cavity. (b) Left ventricular angiogram in hypertrophic cardiomyopathy showing angulation of left ventricular cavity. Left: systolic frame. Right: diastolic frame.

ques⁴³ we showed delay in opening of the mitral valve, indicating abnormal relaxation. Peak filling rate of the left ventricle correlated inversely with this delay. Isovolumic relaxation time was prolonged and this was considered to be a primary abnormality in

hypertrophic cardiomyopathy. End-systolic dimensions were reduced and the rapid filling period tended to be prolonged. The filling pattern was abnormal, due both to impaired relaxation and to abnormal shape of the left ventricular cavity. Previous work by

Fig. 4 Diagrammatic representation of the left ventricle, papillary muscles, chordae, and cusps of the mitral valve in diastole (top) and systole (bottom), as viewed from the transducer of the echocardiograph. The contraction of the hypertrophic ventricular muscle forces the chordae and papillary muscles against the septum, eliminating the cavity. (Reproduced from Gehrke J and Goodwin J F *Clinical Cardiology* 1978; 1: 152-72, with permission of the authors and editors of *Clinical Cardiology*.)

Upton and colleagues⁴⁴ had shown that left ventricular wall movement was incoordinate, patchy, and not uniform.

Hanrath *et al.*⁴⁵ also reported prolonged isovolumic relaxation and a reduction in the rapid filling phase of diastole with an increase in ventricular dimensions.

Alvares⁴⁶ in our laboratory using phonocardiography, apex cardiography, and M-mode echocardiography showed that the normal sequence of events in

diastole is completely disrupted in hypertrophic cardiomyopathy. Aortic valve closure occurred after the minimum dimension of the left ventricular cavity, and the isovolumic relaxation period (from aortic valve closure to mitral valve opening), though often prolonged, tended to be shortened in patients with gradients (Fig. 6). The effects of chronic beta adrenergic blockade were variable. In the majority of patients the active suction period was prolonged, thus aiding ventricular filling, but in the minority was shortened (Fig. 7). These results indicate the variability and incoordination of ventricular diastolic function and thus the difficulty of predicting the effects of any particular drug. They also explain the diverse effects of beta adrenergic blockade.

It is apparent that the diastolic abnormalities in hypertrophic cardiomyopathy are the most important feature of the disease and are exceedingly complex. Far from being uniform, they are patchy and irregular, depending upon the extent and distribution of the myofibrillar lesions. Generalisations as to the exact disorder of the normal filling pattern in any individual patient are likely to be fallacious.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS OF HYPERTROPHIC CARDIOMYOPATHY

When gradients are present the diagnosis can be made at the bedside by three cardinal physical signs. The *ejection murmur* of late onset is heard at the apex, at the left sternal edge, and occasionally at the base of the heart. The *arterial pulse* shows a rapid upstroke and rapid decline and has an ill-sustained or jerky quality. The third sign is the *palpable atrial beat* caused by the strong contraction of the left atrium needed to fill the stiff left ventricle (Fig. 8).

When gradients are present the differential diagnosis must include aortic valvar stenosis, subvalvar stenosis, mitral regurgitation, and ventricular septal defect but when the three major physical signs are present and when there is a family history of sudden death and symptoms of angina, dyspnoea, and syncope a diagnosis of hypertrophic cardiomyopathy can be made reliably at the bedside.

When gradients are absent and there is little if any murmur the diagnosis is much more difficult. The heart may even appear to be normal, though a palpable left atrial beat and jerky pulse are useful clues. Sometimes pulmonary hypertension may be noted because of the high left ventricular end-diastolic pressure.

When there is an apical mid-diastolic murmur, mitral valve disease or left atrial myxoma may be suggested, while when there is mitral valve calcification and atrial fibrillation the differentiation from rheumatic heart disease can often not be made clinically and depends upon angiocardiography. In patients with

Fig. 5 M-mode echocardiogram in hypertrophic cardiomyopathy showing systolic anterior movement of the mitral valve. The slit-like cavity of the left ventricle is almost eliminated in systole by the hypertrophied ventricular muscle and the mitral valve apparatus. The mitral valve cusps are thickened, probably as a result of turbulence of blood flow. (Courtesy of R Alvares, PhD.)

angina but no abnormal physical signs, electrocardiography showing deep T wave inversion, left atrial enlargement, and Q waves may suggest the diagnosis.

It is probable that hypertrophic cardiomyopathy masquerades as other conditions more frequently than is generally realised.

MOST IMPORTANT DIAGNOSTIC TEST

M-mode echocardiography is of value when all the features are present, namely disproportionate septal thickness, apparently poor movement of the septum, reduced systolic diameter of the left ventricle, prolonged diastolic closure rate of the mitral valve, systolic anterior movement of the mitral apparatus, and mid-systolic closure of the aortic valve. But these features can be found singly or even in combination in other conditions.

M-mode echocardiography may fail to show any features of hypertrophic cardiomyopathy in a proven case. This is particularly likely to be the case where septal hypertrophy is localised and particularly asymmetrical and disproportionate.

In my experience the most important diagnostic test is the angiogram (Fig. 3). A detailed analysis of 100 of our patients showed that 90 had either *elimination* of the left ventricular cavity or pronounced narrowing of the mid portion of the ventricle, with angulation of the body. Sometimes contrast medium may be squeezed into the apex and almost isolated from the main cavity (Fig. 9). In six patients

the cavity appeared normal or the papillary muscles merely somewhat prominent. In four patients the cavity was dilated. Characteristic features thus occur in 90% of patients but the disease can exist with almost normal appearances. *Dilatation* of the left ventricle is very rare and when it occurs is likely to be associated with severe widespread disease, extreme mitral regurgitation, or massive myocardial infarction.⁴⁷ Ventricular dilatation does not indicate that hypertrophic cardiomyopathy has progressed to dilated congestive cardiomyopathy, which is an entirely different disease.

EXPERIENCE IN PROGNOSIS: INCIDENCE OF SUDDEN DEATH

My colleagues and I now have experience of 254 patients followed for up to 23 years with a mean of six years. Forty-eight patients died, 32 of them suddenly. The deaths in other patients were mainly the result of congestive heart failure; embolism or infective endocarditis were uncommon causes.⁴⁸ The high incidence of sudden death has been noted by many investigators and was also seen in our previous studies.⁴⁹ Of 119 patients, 69 with a gradient, 30 died, 19 suddenly. In the multicentre study of Shah *et al.*,⁵⁰ in which we took part, of 190 patients, 49 died, 26 suddenly. No definite features predictive of sudden death could be detected at that time, but we now consider that young age (14 years or less), a strong family history, and progressive symptoms are all fea-

Fig. 6 Diastolic time intervals in hypertrophic cardiomyopathy. Aortic valve closure (A2) occurs after the minimum dimension of the left ventricular cavity (Mo, mitral valve opening; O, nadir of apex cardiogram trace; F, end of slow relaxation period, SRP). (See text.) (Reproduced from Alvares R, PhD Thesis, University of London 1980, by permission of the author.)

tures suggesting a bad prognosis. The history, and particularly changes in symptoms, appear to be better predictors of poor prognosis than any haemodynamic or electrocardiographic measurements. Maron *et al.*⁵¹ described families of "malignant" hypertrophic cardiomyopathy with a high incidence of sudden death.

Although sudden death was originally thought to be caused by outflow tract obstruction, attention has recently been given to the possibility of arrhythmia as a cause by Goodwin and Krikler⁵² and by Maron *et al.*⁵³ Krikler *et al.*⁵⁴ described two patients who died suddenly. One patient had documented ventricular fibrillation, the other had both a short PR interval and wide QRS complex, while there was a family history of sudden death in both. At necropsy accessory bypass tracts were seen between the atrium and ventricle on the right side of the septum. Ingham *et al.*⁵⁵ described 13 patients with arrhythmias and conduction defects. Electrophysiological studies showed pro-

longed His-Purkinje conduction. It is probable, however, that ventricular arrhythmias are a more frequent cause of sudden death than supraventricular and that true pre-excitation is unusual in hypertrophic cardiomyopathy. Savage *et al.*⁵⁶ noted ventricular arrhythmias in 50 of 100 patients subjected to ambulatory electrocardiographic monitoring and effort testing.

A relation between sudden death and ventricular arrhythmia has been established by our group.⁵⁷ This study examined the incidence of ventricular tachycardia and sudden death in a 72 hour electrocardiographic monitoring study of 86 patients. During monitoring 23 patients had ventricular tachycardia, 10 having more than three episodes. The patients were followed for between one to four years (mean 2.6 years). Seven died suddenly, and, of these, five had either multiform paired premature ventricular contractions or episodes of ventricular tachycardia. Ven-

Fig. 7 Effects of long term beta adrenergic blockade on diastolic time intervals in hypertrophic cardiomyopathy. The active suction period from opening of the mitral valve to the nadir of the apex cardiogram (Mo—O) is prolonged in most, but not all, patients on beta blockade (hatched columns). (Reproduced from R Alvares, PhD Thesis, University of London, 1980, by permission of the author.)

Fig. 8 Phonocardiogram, carotid pulse tracing, apex cardiogram, electrocardiogram in hypertrophic cardiomyopathy showing the ejection murmur starting after the first heart sound, delayed aortic valve closure (P2, A2), sharply rising ill-sustained arterial pulse, atrial beat (thick arrow), and third heart sound (VG). (Reproduced from R Alvares, PhD Thesis, University of London, 1980, by permission of the author.)

tricular tachycardia was significantly associated with sudden death in older patients who had symptoms. This may or may not be true of younger patients also. There was no significant relation between supraventricular tachycardia and sudden death.

EFFECT OF DRUGS ON ARRHYTHMIA AND PREVENTION OF SUDDEN DEATH

The lack of effect of beta blockade in preventing sudden death has been reported.⁵⁸ In our studies⁵⁰ about 50% of patients who died suddenly were on beta adrenergic blockade. These results and those of others suggest that beta blocking agents do not prevent sudden death. Neither at rest nor on effort did beta blockade alter the incidence of supraventricular or ventricular arrhythmia. A few years ago Krikler and I theorised that the calcium blocking agent verapamil might be more effective than beta adrenergic blocking agents.⁵² But our further study⁵⁹ of verapamil in an ambulatory electrocardiographic investigation showed that there was no significant reduction in the frequency of arrhythmias while on verapamil.

Amiodarone, however, abolished ventricular tachycardia in 10 of 13 patients.⁵⁹ Amiodarone represents a significant advance in the treatment of arrhythmias in hypertrophic cardiomyopathy but we do not yet know whether it has significant haemodynamic effects. It is my impression that amiodarone improves severe cardiac pain, possibly because of its beta blocking action. Arrhythmia may not always be responsible for sudden death. Another possible cause was illustrated by one of our patients, reported by McKenna *et al.*⁶⁰ This patient, while walking to the x-ray department with an escort, and wearing a 24 hour continuous monitor, suddenly

Fig. 9 Left ventricular angiogram by hypertrophic cardiomyopathy showing extreme narrowing of the distal portion of the cavity and almost complete elimination of the apex with isolation of the tip of the ventricle from the proximal cavity. Left: systolic frame. Right: diastolic frame.

complained of feeling faint and lost consciousness. Her pulse disappeared for over a minute before she was resuscitated. In the early stages of the attack tachycardia and ischaemic ST segment changes occurred. In the early recovery phase there was some atrioventricular dissociation and fusion beats, but no bradycardia, cardiac arrest, or ventricular tachycardia or fibrillation. Subsequent tracings during recovery also showed pronounced ST segment depression. On another occasion several episodes of ventricular tachycardia occurred of which she was quite unaware and which did not produce symptoms. Some haemodynamic event had occurred in the left ventricle to produce the syncopal attack and acute ischaemic changes. It is likely that a sudden reduction in ventricular volume was produced by peripheral vasodilatation which resulted in further reduction in filling of the left ventricle, made worse by the tachycardia.

MECHANISMS OF SUDDEN DEATH (Table 1)

These are complex and interactive. They relate both to arrhythmia and to haemodynamic changes. The haemodynamic changes are probably related to acute reduction in left ventricular volume and to resistance to filling of the left ventricle. The end-systolic volume of the left ventricle is smaller than normal and relaxation is prolonged. If the ventricle does not fill adequately, the volume will be further reduced, which will encourage apposition of the massive left ventricular wall to the septum. In this way the cavity of the left

ventricle is *eliminated* (not obstructed) (Fig. 4). The anterior mitral valve apparatus meets the septum and this is how gradients are created. The combination of resistance to filling of the left ventricle, reduced left ventricular volume, and powerful left ventricular contraction together cause a sudden dramatic fall in effective left ventricular outflow. This is the "obstruction" so frequently discussed (Fig. 4).

It follows that measures to prevent sudden death must include antiarrhythmic drugs in patients shown to have arrhythmias by ambulatory electrocardiographic monitoring. In our experience beta adrenergic blocking agents, verapamil, and the usual antiarrhythmic drugs have not been successful. Propranolol has been disappointing, though Frank *et al.*⁶¹ reported reduction in the incidence of death with very large doses of propranolol. But, in our hands, only amiodarone has been successful.

Systemic hypotension, hypovolaemia, and vasodilatation should be avoided, as should undue tachycardia and positive inotropic drugs and manoeuvres. Digitalis is usually better not given, the exception being the presence of rapid atrial fibrillation in which the ventricular rate must be slowed.

BETA ADRENERGIC BLOCKING AGENTS, CALCIUM AGENTS, AND ANTIARRHYTHMIC AGENTS

Treatment should aim at reducing symptoms, preventing sudden death, and retarding the advance of

the disease. These different aspects and the varying patterns of the disease in different patients indicate that treatment must be adjusted to the individual. It is clear that the practice of administering propranolol or other beta blocking agents on a routine basis to all patients is now obsolete and untenable.

Before deciding on the best form of treatment the patient should have a 48 or 72 hour ambulatory electrocardiographic study. If this indicates premature ventricular extrasystoles or runs of ventricular tachycardia then amiodarone should be given in a dose of 600 mg daily for one week, and then 400 daily. If the patient also has symptoms of dyspnoea and angina these may respond to amiodarone alone. If not, propranolol or another non selective beta blocking agent should be given cautiously in addition, starting with a small dose of 10 mg four times daily and increasing carefully. We do not yet have data on the results or risks of combined treatment with amiodarone or beta blockade, so caution is necessary. But theoretically this combination is attractive as it has the twin aims of improving prognosis and relieving symptoms.

If there are no arrhythmias, but symptoms are present, propranolol should be given as the sole drug. If beta adrenergic blocking therapy is not successful, verapamil may be tried. In some patients it certainly improves symptoms, haemodynamics, and exercise capacity,^{62 63} but other patients do badly, as we have noted. Hypotension and lengthening of the PR interval may occur on intravenous administration.^{62 63} Rosing *et al.*⁶⁴ were obliged to discontinue oral verapamil because of sinus arrest and hypotension in one patient after a single dose of 80 mg verapamil, while another patient developed second degree intraventricular block. Two additional patients died; one developed severe chest pain after four doses of 80 mg of verapamil and the other died during operation for septal resection, having previously developed pulmonary oedema on verapamil at a dose of 130 mg six hourly for 13 doses.

The long term effects of verapamil have also been studied.⁶⁴ Of 78 patients, 54% obtained sustained symptomatic improvement over periods of from six to 30 months. Haemodynamic and electrophysiological changes occurred in 19 patients (25%). Three patients died in pulmonary oedema. Rosing *et al.* remarked that verapamil should not be given if there is evidence suggesting pulmonary venous hypertension and that treatment should not be started if the indirect left atrial pressure exceeds 22 mmHg.

Care is obviously necessary in using verapamil and it should not be the first line of treatment, but in patients who cannot tolerate or do not respond to beta adrenergic blocking agents, verapamil may be given cautiously, in doses of 20 mg three times daily,

increasing gradually if no adverse effects occur, to 80 mg four times daily. Larger doses are occasionally employed, but should be used with caution. The objective of verapamil treatment should be improvement in symptoms, haemodynamics, and exercise capacity rather than relief of arrhythmia. We do not have experience of the combination of verapamil and amiodarone because this would be dangerous. Patients should be kept under close observation in hospital when starting verapamil.

Kaltenbach *et al.*⁶⁵ claimed that verapamil reduced left ventricular mass in hypertrophic cardiomyopathy and have suggested that it may be better treatment than beta blocking agents.

It is tempting to hope that propranolol might reduce left ventricular hypertrophy by diminishing the force of contraction of the left ventricle. Though the work of Vaughan Williams *et al.*⁶⁶ showing reduction of rate of growth of the myocardium in small animals given propranolol, there is no clinical evidence to indicate that this happens in man with hypertrophic cardiomyopathy.

The place of other calcium blocking agents such as nifedipine and diltiazem is not known. Nifedipine has been shown to improve diastolic function in acute haemodynamic observations.⁶⁷ Care should be taken with nifedipine because it can produce considerable vasodilatation and hypotension and could thus precipitate syncope.

SURGICAL TREATMENT

Septal resection is indicated in a small group of patients with persistent outflow tract gradients of greater than 50 mmHg, severe symptoms which do not respond to medical treatment, and pronounced septal and papillary muscle hypertrophy. The immediate results are gratifying in terms of relief of symptoms and improvement in haemodynamics but the mortality is high, and there is an incidence of late congestive heart failure after the operation.^{68 69} Kuhn *et al.*,⁷⁰ however, claimed a surgical mortality half that which occurred in patients treated with propranolol.

Mitral valve replacement is indicated for severe intractable mitral regurgitation which occurs as a complication in up to 5% of cases as a result of calcification, turbulence, or infection. Resection of the mitral papillary muscles which is implicit in the operation also removes any systolic left ventricular gradients that may be present.

TREATMENT FOR ATRIAL FIBRILLATION AND CONGESTIVE HEART FAILURE

Immediate cardioversion is required if rapid atrial fibrillation develops. Heparin should be given to prevent embolism. After conversion to sinus rhythm amiodarone may be given as it is likely to maintain the

patient in sinus rhythm, or, if not, to stabilise the atrial fibrillation. Alternatively, a small dose of digitalis may be given along with a small dose of beta adrenergic blocking agent. Amiodarone may be given in conjunction with digitalis but it tends to increase the effects of digitalis on the heart so caution is necessary. Congestive heart failure implies advanced and severe widespread disease that should be treated in the usual way with diuretics which must be used with great care in patients with persistent outflow tract gradients. Vasodilator therapy for heart failure is contraindicated.

When congestive heart failure develops, gradients usually disappear,⁹ but in some patients these may remain. Such patients are all too often intractable therapeutic problems; the risks of surgical treatment are very high and the results poor.

Much has been learned about hypertrophic cardiomyopathy over the past two decades. The impressions gained initially have been revised in the light of new knowledge. Clues as to prognosis are emerging and we can expect treatment to become more rational. The catecholamine theory of causation of hypertrophic cardiomyopathy, while not proven, has much theoretical, circumstantial, and some practical appeal.

Dilated congestive cardiomyopathy

This is a syndrome of dilated ventricles, gallop rhythm, and congestive heart failure, with gross impairment of systolic function. The disease usually involves both ventricles, but a right ventricular variety may occur. The cause or causes are not known. Possible associated or conditioning factors include high and prolonged intake of alcohol,⁷¹ high blood pressure,⁷² pregnancy or the puerperium,^{73 74} and a disorder of cellular immunity resulting from infection.^{75 76} In 1967 a new infective agent was postulated but has not been confirmed.⁷⁷

The pathology yields no clues; the heart is dilated and overweight, but thickness of the ventricular walls is not increased. There are no valvar or coronary artery lesions and histology shows variable degrees of fibrosis. Cellular infiltration suggests a diagnosis of myocarditis. Electronmicroscopical studies show major abnormalities but none to indicate aetiology.

The diagnosis of dilated congestive cardiomyopathy is basically one of exclusion. Heart failure of unknown cause without evidence of underlying heart disease or disease elsewhere in the body sums up the usual presentation. Some patients, however, may be detected before overt congestive heart failure occurs. Gallop rhythm, cardiomegaly, and impaired left ventricular function on echocardiography and nonspecific electrocardiographic abnormalities may disclose an earlier stage of the disease. Though the history is usually

short (six months to two years) sometimes patients have had cardiomegaly for a number of years, indicating a much longer period of development of the disease.

The incidence is largely unknown. Torp⁷⁸ reported 94 cases of verified congestive cardiomyopathy in the years 1970–77 in Malmö, Sweden, which has a population of 250 000. This study was part of the research project on congestive cardiomyopathies of the International Society and Federation of Cardiology.⁷⁹

An association between virus disease and dilated congestive cardiomyopathy has been suggested on many occasions.^{75 76 80} Recently we investigated the levels of Coxsackie virus titres in the blood of patients with dilated congestive cardiomyopathy compared with controls. There was a highly significant increase and very high levels of antibody titres in the cardiomyopathy patients but not in the controls. This difference, however, was confined to those patients with a short history.⁸¹

The explanation of these findings is uncertain. It is possible that the association between high Coxsackie titres and cardiomyopathy is a chance one; alternatively, recent infection is a possible, but unlikely, explanation since the endomyocardial biopsy in those patients in whom it is performed did not show any evidence of inflammatory lesion. The most likely explanation in my view is that the infection creates an autoimmune process which leads to progressive myocardial damage. Fowles *et al.*⁸² reported a disorder of cellular immunity in patients with dilated congestive cardiomyopathy, but Trueman *et al.*⁸³ did not find any difference between controls and patients with congestive cardiomyopathy by immunofluorescent techniques, denying the claims of Bolte.⁸⁴ An association between myocarditis and cardiomyopathy has been suggested⁸⁵ in a description of 10 patients with rapid onset of congestive heart failure of unknown cause apparently resulting from early congestive cardiomyopathy. In all patients, however, endomyocardial biopsy showed evidence of inflammatory myocarditis. Nine were treated with prednisone and azathioprine, and one with prednisone alone. Five improved, though one died later, and four did not deteriorate. Evidence of improvement was based on non-invasive studies and on invasive investigations and biopsy.

A possible sequence of events is shown in Table 2. Acute virus myocarditis results in complete recovery in the vast majority of patients but in a small percentage heart failure may occur acutely, persist, and be indistinguishable from cardiomyopathy except by endomyocardial biopsy. In other patients there may be a latent period after apparently full recovery during which the autoimmune process develops and results in the established syndrome of cardiomyopathy years

Table 2 *Viral myocarditis and cardiomyopathy*

later. Alternatively, some patients may have a genetically determined deficiency in cellular immunity which renders them liable to virus attack on the heart. Further work is needed to confirm or refute these hypotheses⁸⁶ which are attractive because they open the mind to the possibilities of treatment.

TREATMENT OF DILATED CONGESTIVE CARDIOMYOPATHY

Treatment is unsatisfactory and will remain so until the causes of the diseases are identified. At the present time general measures such as avoidance of smoking and alcohol and reduction of effort are basic. Experience without proof indicates that the suggestion of Burch *et al.*⁸⁷ of prolonged bedrest has some merit.

The usual measures for congestive cardiac failure are required. Digitalis is needed if atrial fibrillation is present and may be prescribed in sinus rhythm, but it is uncertain whether there is any benefit after the first few months of treatment.^{88,89} Some improvement may be obtained by the use of vasodilators and inotropic agents. We have found hydralazine to be effective but large doses are needed and side effects are not rare.⁹⁰ Isosorbide or prazosin can be used as an alternative to hydralazine. Salbutamol⁹¹ is of value by intravenous infusion in critical severe heart failure, mainly because of peripheral vasodilatation and unloading of the left ventricle but also because of some positive inotropic effects. The tachycardia so produced is a disadvantage, and tachyphylaxis is common. Increase in blood sugar and fall in serum potassium are also disadvantages. Positive inotropic agents such as dobutamine may be used. In extreme situations a combination of nitroprusside with dobutamine may produce improvement, but all too commonly this is only transient. Other vasodilators and new inotropic agents are under investigation.

Anticoagulants are indicated if the patient is confined to bed with oedema or if there is atrial fibrillation.

Beta adrenergic blockade

This controversial treatment has been suggested by workers in Gothenburg in Sweden.⁹²⁻⁹⁴ They claimed

clinical and haemodynamic improvement after graded doses of metoprolol. It has been suggested that patients with disproportionate tachycardia who may thus have an excess of catecholamines in the heart may be those most suitable for treatment, but a study from our department⁹⁵ did not show any increase in plasma noradrenaline or in sympathetic function before overt heart failure had occurred, though parasympathetic function was impaired. Certainly slowing of the heart and reduction in oxygen demand might be of value. By contrast with the results of the Swedish investigators, Ikram and Fitzpatrick⁹⁶ found no benefit from beta adrenergic blockade treatment, but many of their patients (71%) had possible alcoholic cardiomyopathy and were less severe symptomatically than the cases of Swedberg *et al.*⁹⁴ In addition, they used a different agent, and the duration of treatment was shorter. The matter is still undecided and further trials are necessary.

The results of the studies by Mason *et al.*⁸⁵ suggest that when the duration of heart failure is short (a year or less) and the endomyocardial biopsy shows evidence of inflammatory action, steroids and immunosuppressive drugs may be of benefit. Steroids have not been shown to influence the course of typical congestive cardiomyopathy⁹⁷ and when given in acute myocarditis may exacerbate the condition.

Previous work has suggested that patients with appreciable ventricular hypertrophy tend to live longer than those with less; that possibly the agent or agents that affect the myocardium have interfered with contractile function by preventing the binding of calcium by troponin. The result of impairment of contractile function could be ventricular dilatation, increased wall tension, and failure of the DNA/RNA interaction that is needed for hypertrophy.^{10,11}

Swedberg *et al.*⁹³ have suggested that prognosis is improved by beta adrenergic blockade therapy but no definite prognostic improvement has been reported from other methods of treatment though our studies have shown that there was a slight benefit in patients treated in the past two to five years, perhaps as a result of earlier diagnosis and vasodilator treatment (MacArthur *et al.*, to be published).

Restrictive/obliterative cardiomyopathy

Restrictive/obliterative cardiomyopathy is usually caused by endomyocardial fibrosis, either of the tropical variety with little or no eosinophilia or of the temperate zone type with intense eosinophilia, as described by Loeffler in 1936.¹⁵ These two conditions have been regarded as one and the same by Olsen and Spry⁹⁸ and have been named Loeffler's endomyocardial disease by the WHO/ISFC task force.⁶ Nevertheless, though the pathological features are identical and

the clinical and haemodynamic abnormalities closely similar, differences do exist between the two conditions. There is the absence of significant eosinophilia in the tropical type of endomyocardial fibrosis, the climatic differences, and the incidence of tropical endomyocardial fibrosis in the rainy season. There is no climatic incidence or seasonal variation in Loeffler's endomyocardial fibrosis of temperate climate as far as is known.

It has been suggested⁸⁶ that the endocardium reacts in the same way to different irritants, producing the exudative reaction leading to fibrosis and thrombosis, with changes in the small intramyocardial vessels that is characteristic of endomyocardial fibrosis. Scarring of the myocardium results and in the late stages fibrous tissue and thrombus progressively obliterate the ventricular cavity and increase the resistance to inflow.

A possible irritant that has been extensively studied is the eosinophil. Clones of circulating eosinophils in Loeffler's endomyocardial disease have structural abnormalities. They are vacuolated and degranulated. The granules are abnormal and may release products which damage the endocardium.⁹⁹ There is abnormal binding of IgG coated erythrocytes. A third of the abnormal eosinophils ingest red blood cells that are coated with complement as compared with less than 1% in normal subjects. Also eosinophil kinetics are abnormal and their half life is twice normal. Prolonged retention of eosinophils in the circulation may be an important factor in endomyocardial damage.^{98 99}

It may be that the rogue eosinophil is also the cause of tropical endomyocardial fibrosis and studies sponsored by the ISFC are in progress to investigate this.

TREATMENT OF ENDOMYOCARDIAL FIBROSIS

Treatment is unsatisfactory. Attempts to control profuse eosinophilia by means of steroid and immunosuppressive therapy and by antimetabolic drugs have not been strikingly successful,¹⁰⁰ except in acute exacerbations of the disease. Treatment for heart failure is only partly successful because systolic function remains good until a fairly late stage, while severe mitral and tricuspid regurgitation may dominate the picture. Improvement has been achieved by surgical means, consisting of resection of the endomyocardial fibrous tissue and thrombus, and replacement, when needed, of the atrioventricular valves.¹⁰¹⁻¹⁰³ Early results are satisfactory but the long term prognosis is uncertain. Three patients have been treated surgically at the Royal Postgraduate Medical School and have done well initially.¹⁰⁴

AMYLOID HEART DISEASE

Although rare, amyloid heart disease is an intriguing entity. Because of its distribution around the small

blood vessels in the myocardium it produces a stiff unyielding muscle mass; the "stiff heart".¹⁰⁵

The rigid myocardium causes abnormalities of filling, some of which resemble constrictive pericarditis and restrictive cardiomyopathy. Differences do exist, however, especially in the pattern of ventricular filling. Filling is slow throughout diastole in contrast to endomyocardial fibrosis in which ventricular filling is initially rapid and then becomes slow. This difference explains the absence of a left ventricular third heart sound in amyloid heart disease.¹⁰⁵

Nevertheless, clinical similarities to constrictive pericarditis or restrictive cardiomyopathy do exist, especially in the pattern of the jugular venous pulse, and amyloid disease should be considered in the differential diagnosis especially if there is cardiac pain.

I have presented some hard data, much personal experience and conviction, and a deal of speculation. I make no apology for the last for it is the business of clinical research workers to ask questions as well as to answer them.

I speculate that hypertrophic cardiomyopathy is an endocrine disorder; that congestive cardiomyopathy is a disease of cellular immunity set up by a previous virus infection; that restrictive/obliterative cardiomyopathy is a disorder of immunity of the eosinophil.

There are many problems to be resolved and the prospects may seem daunting, yet they are, in fact, exciting and challenging and I am sure we will have the answers by the end of the century, though we shall require the collaboration of experts in many fields: immunologists, cell biologists, endocrinologists, biochemists, geneticists, and others.

No longer are the cardiomyopathies the province of the cardiologist alone for their frontiers extend deep into the realms of general internal medicine, pathology, and immunology.

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