Jubilee Editorial

Hypertrophic cardiomyopathy

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When I first used the expression "cardiomyopathy" in 1956 I did not realise that I had coined a term that would become widely applied. Experience, however, has confirmed its value in describing isolated non-coronary, non-hypertensive, and non-valvar myocardial disease, especially when used with an adjective if the aetiology or morphology is sufficiently clear. Some authorities prefer to restrict its use to disorders of the myocardium of unknown cause; this would exclude hypertrophic cardiomyopathy which in most patients is an inherited disorder. Although the division into hypertrophic and congestive cardiomyopathies has proved helpful, classification remains somewhat unsatisfactory despite many worthy attempts to clarify the position.

Unexplained and isolated myocardial hypertrophy was described in the nineteenth century by German pathologists and an obstructive element was recognised in their reference to "conus stenosis". Two patients with massive hypertrophy were reported in 1907 by Schminke who considered that hypertrophy led to further hypertrophy.² Several papers were published in the 1930s and 1940s under various titles describing isolated myocardial hypertrophy, and Evans's paper on "familial cardiomegaly" in the *British Heart Journal* was particularly important.³ He described nine patients seen at the London Hospital and emphasised the diagnostic importance of a family history of similar disease, frequent arrhythmias, and a tendency to sudden death. Brock later added another facet to the story in suggesting the possibility that hypertrophic muscle was responsible for obstruction.⁴ He had observed and was impressed by apparent obstruction of the outflow tract by hypertrophic muscle after pulmonary stenosis had been relieved by valvotomy and he later described apparently important muscular obstruction in the left ventricle. Teare, a forensic pathologist, followed with a description,

also in the *British Heart Journal*, of asymmetric septal hypertrophy found at necropsy in seven subjects who had died suddenly.⁵

Thus the strands of medical knowledge were converging and pointing to a distinct disease entity that was characterised by an apparently idiopathic isolated and often asymmetric myocardial hypertrophy, possibly obstructive, occurring in families, and with a tendency to cause sudden death. A spate of papers followed in the early 1960s describing the clinical, electrocardiographic, angiographic, and haemodynamic features of this condition. Contributions from Braunwald and his colleagues at the National Institutes of Health, Bethesda^{6,7} and from Goodwin and colleagues at Hammersmith Hospital⁸⁻¹⁰ were most important, but they used different names—idiopathic hypertrophic subaortic stenosis in the United States and hypertrophic obstructive cardiomyopathy in the United Kingdom. Neither term recognised the familial factor and both emphasised obstruction which often is not present. McMichael found 12 names for this condition in 1964¹¹; I think there were more, illustrating the principle that the number of names is directly related to the obscurity of the condition.

Criley and others criticised the concept of obstruction on various grounds including the evidence of striking dynamic lability, the effective rapid discharge of ventricular volume in early systole, and the low end systolic volume, even in some of the most severe cases.¹² These points, however, do not deny an obstructive element because coexistent mitral reflux could explain these findings. The triad of cardiac pain, faintness or syncope on exertion, and dyspnoea on exertion in patients who have severe disease certainly suggests obstruction, especially when combined with large intraventricular gradients, albeit variable and of functional origin. Very large gradients seem to be associated with early mitral-septal contact. I find the argument about obstruction a specious one. In this disease, however, the array of symptoms, unlike the signs, does not

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closely match the abnormal morphology and dynamic function. Most cardiologists have been more impressed by the haemodynamic abnormalities caused by abnormal diastolic filling than by the abnormal systolic features of the condition. I have seen a patient with hypertrophic cardiomyopathy develop a paroxysm of atrial fibrillation resulting in profound hypotension and syncope followed by recovery with the spontaneous restoration of sinus rhythm. The paralysis of atrial transport by fibrillation assumes great importance in patients with thick stiff ventricles and may cause severe hypotension and even syncopal death.

Abnormal signs

Abnormal signs range from none in the mild symptom free case to those which closely reflect abnormal dynamic function. Diastolic dysfunction is underlined by finding the physical signs of vigorous atrial systole, such as a prominent "a" wave in the jugular venous pulse or a short low-pitched diastolic murmur enhanced by inspiration from impeded tricuspid inflow. I remember a discussion at the National Heart Hospital nearly thirty years ago about a child who appeared to have severe tricuspid stenosis and strange unexplained left ventricular hypertrophy. Eponyms abounded, including Bernheim and Ebstein, to explain the findings which included giant atrial P waves. Subsequent necropsy showed gross septal hypertrophy and normal valves. Systolic murmurs, most commonly in late systole though not engulfing the aortic second sound, often led to an erroneous diagnosis of aortic valve stenosis or even mitral reflux. On the other hand, the occasional truly late systolic murmur or pansystolic murmur caused by mitral reflux was thought to be of valvar origin. It is thus not surprising that this condition was only recognised by clinicians some 25 years ago—in view of its pleomorphic presentation and mimicry of so many other kinds of heart disease.

Arrhythmias

Arrhythmias are common and the tachycardias particularly so. Frequent ventricular extrasystoles and ventricular tachycardias may presage sudden death. On the other hand, prolonged phases of such disturbance may be followed by a slow spontaneous regression to periods free of arrhythmia; nevertheless, frequent ventricular arrhythmias should be suppressed by appropriate medication in view of their association with deterioration or sudden death. A galaxy of rhythms was recorded over some ten years in one of my patients who first presented at the age of 15 with apparently simple idiopathic paroxysmal

tachycardia, but three years later a firm diagnosis of hypertrophic cardiomyopathy was made when ventricular extrasystoles were frequent; and in her mid twenties asymptomatic complete heart block developed.

Echocardiography

The development of echocardiography in the 1960s stimulated further research and proved to be of considerable diagnostic value, enabling wall thickness and movement as well as valve motion to be assessed and studied *seriatim*. Some overdiagnosis occurred, as is usual with new tools in biological research. The strange systolic movement of the anterior mitral valve cusp has proved of diagnostic value and added credibility to the angiographic appearance of outflow obstruction caused by apposition of the mitral leaflet and septum. The mechanism of this movement remains obscure and although a Venturi effect is possible abnormal dynamic function of thick papillary muscle seems more likely. Premature closure of the aortic valve may be seen and is clearly related to rapid early ejection ending at the time of mitral-septal contact. Echocardiograms are valuable for studying apparently unaffected relatives of a proband and have shown that mild forms of cardiomyopathy are not uncommon and are consistent with leading a normal life. Echocardiography enhances, but certainly does not replace, clinical assessment in this condition any more than it does in any other disease.

Genetic origin

Genetic origin of hypertrophic cardiomyopathy is now widely accepted and almost all clinical accounts describe a familial nature that is sometimes traceable through several generations. Echocardiography has enabled the assessment of relatives by a test that is not only non-invasive but also is sometimes positive when electrocardiograms and x-rays are equivocal or even normal. Elegant studies on the familial nature of the disease by Emanuel and colleagues have confirmed the autosomal dominant nature of its inheritance.¹³⁻¹⁴ They also showed that current techniques for detecting the disease might not give positive results before early adult life. There are sporadic cases that fulfil all the criteria for diagnosis but these do not deny a genetic aetiology. The percentage of isolated cases in any series is likely to be erroneously high for many reasons. A simple negative response when inquiries are made of the patient's family must be queried, especially if relatives have died unexpectedly, because there is an understandable tendency to withhold disquietening

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information from younger, apparently healthy members. Adoption unknown to one of my patients whose real mother had died in the puerperium was the reason for negative information, and another "sporadic" case subsequently had an affected child. Possibly some sporadic cases are caused by a recessive gene.

Pathology

The pathology of this condition has been extensively described and discussed during the past three decades. The distribution of hypertrophy may be generalised or regional (commonly in the anterior basal part of the septum or rarely confined to the free wall). Although morphology correlates well with dynamic function and physical signs, gross appearances do not correlate closely with symptoms in this condition. There should be no dispute about facts, but pathologists like clinicians tend to disagree about their interpretation. I refer to the specificity, or otherwise, of the myocardial disarray that is found in almost all cases. It seems that some minor degree of disarray occurs in secondary hypertrophy and this sign is therefore not specific, but in hypertrophic cardiomyopathy there is very extensive disorganisation of large muscle bundles as well as disarray between fibres and small whorls of muscle; furthermore there is even disorganisation of fibrils within a single cell. Organ abnormality such as visceromegaly, congenital defects, and evidence of endocrinopathy, other than as an effect of heart failure or embolism, are conspicuously absent at necropsy. There have been, however, a few reports of a familial hypertrophic cardiomyopathy associated with a mitochondrial abnormality affecting skeletal muscle.

Treatment

Treatment is essentially unsatisfactory because so far the hypertrophic process has not been reversed, but symptoms and possibly the course of the disease may be modified favourably. The great variation in symptoms and severity of this condition demands the tailoring of treatment to the individual patient. The β blockers became generally available at about the same time as the disease became more widely recognised; and in the early sixties these agents seemed heaven-sent. Here was a drug that would slow the heart, reduce contractility, and block the apparently excessive catecholamine drive. Although β blockers have not fulfilled that early promise in hypertrophic cardiomyopathy, nevertheless, propranolol may relieve or greatly reduce some symptoms, especially cardiac pain, in at least 50% of

patients and so it remains the drug of first choice except when arrhythmias are a prominent feature. Amiodarone, unlike the calcium antagonists and β blockers, is remarkably effective in reducing the frequency and impact of both ventricular and supraventricular tachycardia. There is some evidence that amiodarone together with the cautious addition of a low dose β blocker is better than either alone in controlling symptoms in the most severely affected patients. Heart failure should not be treated with drugs which lower systemic pressure by vasodilatation because this will increase the obstructive factor; also diuretics should only be used with caution.

Surgical treatment

Surgical treatment by myotomy or myomectomy was, like the β blockers, introduced in the early 1960s. There is general agreement that operation should be restricted to those patients with severe symptoms that are unresponsive to medical treatment and with evidence of a large outflow tract gradient. The immediate surgical mortality is high and congestive cardiac failure is not uncommon in the late postoperative period. Severe mitral reflux may develop in hypertrophic cardiomyopathy and should be treated by valve replacement. The results are not as satisfactory as in primary valve disease. But, not surprisingly, outflow tract gradients are abolished and symptoms are sometimes improved.

Course

The course of this disease is ill defined and extremely variable, hence prognosis is particularly difficult. Death is often unexpected and its suddenness a cause for comment in most accounts of the disease over the past thirty years. Those patients with a family history of sudden death and evidence of ventricular arrhythmias are certainly at great risk of syncopal death. It is of interest, however, that not all sudden death in this disorder is caused by arrhythmia. On the other hand, some symptom free patients with minimal disease achieve a normal life span. I have seen symptom free but quite severe hypertrophic myopathy in a patient in his seventies, restricting symptoms in a patient of seven, and unexpected death at the age of eleven. Congestive heart failure often associated with atrial fibrillation may develop in those who survive with a long history of severe disease. Outflow tract gradients then tend to diminish and morphologically there may be patchy thinning of the hypertrophic myocardium, possibly caused by infarction or fibrosis in areas of reduced perfusion; thus in the late stages a differential diagnosis between this extraordinary disorder and non-

hypertrophic cardiomyopathy may prove very difficult.

The ever increasing knowledge of disease continually reveals new problems and thus widens the scope of our ignorance. Hypertrophic cardiomyopathy is no exception, since the capacity of a highly specialised tissue such as myocardium to grow beyond its allotted size is as remarkable a biological phenomenon as the timely cessation of normal growth. When increased resistance to contraction is the stimulus for myocardial hypertrophy the result is mostly homoeostatic and comprehensible, but what of apparently purposeless and almost chaotic hypertrophy? We know that there is usually a genetic fault but we know nothing of its origin or of its translation into pathogenesis. It is not surprising therefore that we have not yet found a means of reversing this extraordinary disorder.

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