INTERNATIONAL LECTURE

Prospects and Predictions for the Cardiomyopathies

By J. F. Goodwin, M.D., F.R.C.P., F.A.C.C.

Additional Indexing Words:
- Idiopathic hypertrophic subaortic stenosis
- Beta-adrenergic blockade
- Catecholamine
- Friedreich’s ataxia
- Left ventricular hypertrophy
- Congestive cardiomyopathy
- Propranolol
- Practol
- Beta-adrenergic stimulation
- Left ventricular outflow obstruction
- Pompe’s disease
- Chagas’ disease

IN THIS LECTURE I shall attempt to survey the current important problems in the commonest forms of cardiomyopathies and suggest avenues along which research may profitably proceed in the future.

The classification of the cardiomyopathies into hypertrophic, congestive, obliterative, and restrictive has the advantage of allowing a study in depth to be made of the pathological, functional, and clinical features of these types without prior knowledge of their etiology. The classification also assists the identification of various forms of cardiomyopathy in circumstances where causal factors are being sought.1

Figure 1 shows the four types in diagrammatic form. The general characteristics of each type are well known. In the hypertrophic form there is massive ventricular muscle hypertrophy with reduction in end-systolic volume and often a concentration of hypertrophy in the region of the septum forming the asymmetrical bulge that inspired Teare2 to name the condition “Asymmetrical hypertrophy of the heart.” With this concentration of the disease in the region of the septum there is commonly a gradient in systole across the outflow tract and the condition is then usually known as Hypertrophic Obstructive Cardiomyopathy or Idiopathic Hypertrophic Subaortic Stenosis (IHSS). In about 10 to 20% of patients, however, no gradient is discernible either at rest or on provocation and the disorder is then termed Nonobstructive Hypertrophic Cardiomyopathy. Opinion is divided as to whether these two conditions are basically the same disease or whether they are different entities, but in my view the evidence points strongly to their being different facets of the same disease.

The congestive type of cardiomyopathy is characterized by considerable dilatation of the left ventricle but moderate hypertrophy. The contractile function of the heart is severely damaged and the heart has very poor pump function. No obstructive element is present in this type.

The obliterative type embraces Endomyocardial Fibrosis of humid tropical zones and Löeffler’s eosinophilic cardiomyopathy of temperate zones, but it has been suggested that these two conditions are basically the same disease.3 Here the ventricular cavities, notably the inflow tracts, become obliterated by fibrous tissue and added thrombus.

The restrictive type is characterized by stiff muscle without marked hypertrophy, as in amyloid disease.

Hypertrophic Cardiomyopathy

The pathology of this condition is now well recognized and the characteristic lesion is grossly hypertrophied, short, thick, fragmented muscle fibers concentrated in circular arrangements, or whorls, with large nuclei and perinuclear spaces. The abnormal myocardial fibers may be interrupted by fibrous tissue which arises within the myocardial fibers and spreads toward the surface, replacing a variable amount of muscle tissue, which results in shortening of the fiber and its termination in collagen tissue.4

In the original observations of our group5 many instances of irregular cellular contraction, with some

From the Division of Cardiovascular Disease (Clinical Cardiology), Department of Medicine, Royal Postgraduate Medical School and Hammersmith Hospital, London, England.

This paper is based on the International Lecture of the American Heart Association, delivered at the 25th Annual Meeting in Atlantic City, New Jersey, November, 1973.

Address for reprints: Dr. J. F. Goodwin, Clinical Cardiology, Royal Postgraduate Medical School, Hammersmith Hospital, London W12, England.
Cardiomyopathies

were found, but the possibility of an artifact being responsible was not excluded. Ferrans, Morrow, and Roberts observed a number of abnormalities of myofibrillar structure, localized in the Z bands, consisting of widening and spreading of the Z band material toward the center of the sarcomere, splitting of Z bands and attachment of Z bands to the sarcolemma, with increased amounts of material similar to that of the Z bands at points of attachment of myofibrils to intercellular junctions. Their description was in agreement with previous observations, and they also noted alterations in myofibrillar orientations which were considered unique to IHSS. Both branched and unbranched cells contained areas with obliquely or transversely oriented myofibrils. The pattern of myofibrillar organization ranged from entirely normal in some cells to severe disarray in others with immediately adjacent myofibrils orientated perpendicular to each other. In addition, myofilaments that originated from a single Z band sometimes crossed in different directions and were inserted into several different Z bands, resulting in a cross-weaving pattern.

Ferrans et al. noted that formation of new sarcomeres in the usual types of cardiac hypertrophy was not associated with the abnormal myofibrillar orientation found in hypertrophic cardiomyopathy. A disordered arrangement of myofibrils is, however, characteristic of embryonic cardiac muscle in which myofilaments in early developing myofibrils radiate in several directions from a single Z band. Furthermore, branching of myofibrils is found in primitive hearts and disorientation of myofibrils and cross-weaving of myofilaments are a feature of salamander hearts and also of habdomyoma. Ferrans and his colleagues point out that the myofibrillar arrangements in IHSS suggest a less differentiated cell type than that normally found in adult myocardium. They further quote the work of Manasek who has suggested that myofibrillar alignment within specific regions of the heart is a result of response to the stresses induced by contraction. Contraction induces linear stresses within the cell and myofibrillar alignment eventually coincides with these forces. Mechanical forces determine patterns of orientation of other structures such as bones or tendons. Myofibrillar orientation therefore might be assumed to be altered when mechanically oriented forces are abnormal, as in IHSS, or not fully developed, as in embryonic hearts. The abnormal architecture of the myofibrils may prevent the normal alignment of muscle cells necessary for normal development and effective contraction. When the myofibrils are contracting at abnormal angles to other cells they may exert tension upon them, so while some cells shorten others may remain isometric or even stretched. Presumably such a situation would be a powerful stimulus to hypertrophy and might also be implicated in irregular contraction and difficulty in relaxation. If the orderly alignment of cells laid down in the developing heart does not proceed in the usual way then irregular contraction may develop and this in itself may predispose to further abnormal orientation of the developing muscle fibers. Figure 2 shows a suggested sequence of events in the development of hypertrophic cardiomyopathy based on my understanding of the work of Ferrans and his colleagues.

Once massive hypertrophy has developed, it may be expected further to impair relaxation and reduce the rate of ventricular filling. Impaired rate of ventricular filling has already been demonstrated by Stewart and his colleagues while Ziady, working in our laboratory, has shown that the isovolumic relaxation time of the left ventricle is significantly longer.

**Figure 1**

Diagram of the four principle types of cardiomyopathy.

*Circulation, Volume 50, August 1974*
than normal and markedly increased as compared with congestive cardiomyopathy (fig. 3). (G. M. Ziady, personal communication, 1973.) It is probable that problems of filling the grossly hypertrophied left ventricle with its reduced end-systolic size are the most important features of the disease.\(^1\) Although outflow tract systolic pressure gradients are common in the disease and occur in approximately three quarters of the cases, either as a permanent feature or episodically on provocation, it is probable that these features do not principally determine the prognosis.

Studies of the effects of beta-adrenergic stimulating drugs and beta-adrenergic blocking agents on the symptoms and signs of hypertrophic obstructive cardiomyopathy have added further information on diastolic function in hypertrophic cardiomyopathy.\(^8\) Whereas atrial pacing up to 116 beats per minute caused a fall in left ventricular end-diastolic pressure, isoprenaline (which produced less increase in heart rate) caused a marked rise in left ventricular end-diastolic pressure. These results suggest that positive inotropic action due to sympathetic stimulation has an adverse effect on diastolic function and appears to increase the rigidity and reduce the distensibility or compliance of the ventricular muscle.

Webb-Peploe and his colleagues showed that practolol produced an increase in end-diastolic volume in association with the decrease in end-diastolic pressure, an effect not seen in other forms of heart disease which suggests improved distensibility or increased compliance of the left ventricle. Also, the same cardiac work was achieved at a lower left ventricular end-diastolic pressure. More recent studies by echocardiography of ventricular diameters by Ziady in our laboratory have shown the reduction in end-diastolic and end-systolic diameters after beta-adrenergic blockade (personal communication, 1973).

The left ventricular ejection time is prolonged both by hypertrophic cardiomyopathy and by beta-adrenergic blockade. The isovolumic relaxation time is increased in hypertrophic cardiomyopathy and is shortened by beta-adrenergic blockade and this shortening tends to counteract the prolongation of ventricular ejection time leading to a more favorable diastolic filling pattern.\(^9\) Figure 4 shows the effect of practolol on the relationship of left ventricular stroke work index and left ventricular ejection time index in seven patients with hypertrophic cardiomyopathy and in five control patients. It can be seen that in all but two of the patients with hypertrophic cardiomyopathy the left ventricular stroke work index is increased, despite the increase in ejection time, indicating that practolol permits better ventricular filling.

Figure 5 shows diagrammatically the more favorable diastolic pressure-volume relationships in hypertrophic cardiomyopathy after beta-adrenergic blockade and the unfavorable influence of beta-adrenergic stimulation.

These results encouraged us to carry out a trial of beta-adrenergic blocking agents on the symptoms and signs of hypertrophic obstructive cardiomyopathy. A double-blind trial was carried out using a placebo, practolol, and propranolol.\(^10\) Three hundred twenty milligrams propranolol daily, 800 mg practolol daily, and a placebo were administered in four week periods in a double-blind manner to 16 patients. The symptoms were assessed using a diary card and a scoring

![Figure 3](image-url)

**Figure 3**
Isovolumic relaxation time in normal subjects, patients with hypertrophic obstructive cardiomyopathy (HOCM), and congestive cardiomyopathy (COCM). Relaxation time is appreciably longer in hypertrophic cardiomyopathy than in the other two groups. (Courtesy of Dr. G. Ziady.)

![Figure 4](image-url)

**Figure 4**
Left ventricular stroke work index (LVSWI) and left ventricular ejection time index (LVETI) in patients with hypertrophic cardiomyopathy (HOCM) (filled circles) and normal patients (control group) (open circles). It will be seen that in hypertrophic cardiomyopathy beta-adrenergic blockade with practolol (20 mg i.v.) produces an increase in left ventricular stroke work index and also in ejection time index. (Courtesy of Dr. T. Hardarson.)
method. Clinical examination, phonocardiography, and apex cardiography were carried out. The results indicated that dyspnea was improved only in patients with severe limitation, but angina became less frequent with both beta-adrenergic blocking agents, though more strikingly with propranolol. The left ventricular ejection time index was significantly prolonged with propranolol but not with practolol. Both drugs significantly reduced the “A” wave of the apex cardogram and the isovolumic relaxation time.

The results suggested improved ventricular distensibility. Though the possibility that the reduction in the size of the “A” wave might have been due to reduction of atrial drive has to be considered, in view of the results in acute observations, it seems more likely that long term oral beta-adrenergic blocking agents do improve ventricular distensibility.

The Relationship of Catecholamine Disorder to Hypertrophic Cardiomyopathy

It is now relevant to examine the evidence for a neural crest origin or catecholamine abnormality in hypertrophic cardiomyopathy. There are a number of features which suggest that there may be some connection. First, there is the association with systemic hypertension, which, although rare, was described by Brock who first recognized the disease at surgery in 1957. Second, there is the finding by Everson Pears of excessive noradrenosis in the left ventricular outflow tract and although this has not been confirmed, it has not been completely disproved. Further studies using improved techniques may elucidate this.

Third, more persuasive arguments for an association between excessive catecholamine action and the myocardial abnormality stem from the hemodynamic studies already quoted. Lastly, there is an association between pheochromocytoma, neurofibromatosis, and lentiginosis. We have seen one patient with pheochromocytoma and another with cutaneous neurofibromatosis.

Recently Polani and Moynihan have described a syndrome of multiple symmetrical lentigines and left-sided obstructive cardiomyopathy with associated retardation of growth and sometimes intellectual impairment. They suggested that the pathogenesis of the disorder might represent an extensive dysfunction of pigment and other elements of neural crest origin. It was postulated that hypertrophic cardiomyopathy is related to a defect of neural crest origin either primarily, because the neural crest contributes to heart structures, or secondarily, through the lentigines, perhaps by a biochemical mechanism, for it has been suggested that all examples of adrenergic- and noradrenaline-producing cells ultimately have a neural crest origin. Brock has hinted at the presence of a control mechanism in the outflow tract of both ventricles. Thus, on the available evidence, it seems possible that both the abnormal arrangement of cells in the myocardium and the functional disturbances in systole and diastole might be the result of abnormal sympathetic stimulation through a developmental abnormality in the neural crest, an excessive production of catecholamines, or an abnormal response of the developing heart muscle to circulating catecholamines.

The similarities between the cardiomyopathy of Friedreich’s ataxia (in which an autonomic disturbance is postulated) and hypertrophic cardiomyopathy might add further evidence and will be discussed later. However it must be remembered that the majority of patients with hypertrophic cardiomyopathy do not show any overt evidence of catecholamine abnormality. Thus, in our experience, 3-methoxy-4-hydroxymandelic acid (VMA) excretion is normal, hypertension is absent, and there is no evidence of excessive circulating catecholamines or excessive adrenal medullary function. Furthermore, the mental retardation mentioned by Polani and Moynihan and thought possibly to be due to abnormal catecholamine supply or function is characteristically absent in hypertrophic cardiomyopathy. Nor is hypertrophic cardiomyopathy commonly associated with any abnormality of physique or skin pigmentation.

However, both the syndrome described by Polani and

The effect of pharmacological interventions on pressure-volume relationships in hypertrophic obstructive cardiomyopathy (HOCM). Beta-adrenergic blockade increases diastolic volume and reduces diastolic pressure while beta-adrenergic stimulation increases pressure and reduces volume. The effects suggest an increase in stiffness and reduction in distensibility of the left ventricle after beta-adrenergic stimulation and an increase in distensibility and reduction in stiffness after beta-adrenergic blockade.
Moynihan and hypertrophic cardiomyopathy appear to be inherited on a similar genetic basis.

Further work is necessary on the catecholamine content of heart muscle in hypertrophic cardiomyopathy and into other aspects of the association between catecholamine excess and the etiology of the disease.

Does Secondary Hypertrophic Cardiomyopathy Exist as an Entity?

The first description by Brock of what we now recognize as hypertrophic obstructive cardiomyopathy was related to a patient with severe systemic hypertension, and he regarded the muscular hypertrophy of the outflow tract of the left ventricle that produced the obstruction as being secondary to the hypertension. Since then, speculation that either excessive afterload on the left ventricle or fixed outflow tract obstruction might produce hypertrophic cardiomyopathy has been rife. The demonstration of an inappropriate degree of hypertrophy with the clinical and hemodynamic characteristics of hypertrophic cardiomyopathy in association with a mild degree of fixed outflow tract obstruction in the form of valvar aortic stenosis or discrete subvalvar aortic stenosis has been noted in three patients in our experience. Apart from the association with fixed outflow tract obstruction of the left ventricle or systemic hypertension, hypertrophic obstructive cardiomyopathy has been described also in two other apparently unrelated conditions associated with severe cardiac hypertrophy. These are Friedreich’s ataxia and Pompe’s disease. Although massive ventricular hypertrophy involving the septum and papillary muscles, with gross cardiomegaly is recognized in Pompe’s disease, the histology is typical of glycogen storage disease with vacuolation of cardiac muscle cells due to glycogen infiltration, giving a typical lattice work appearance, but no evidence of the typical histological and electron microscopic appearances of hypertrophic cardiomyopathy.

A number of descriptions of massive hypertrophy and obstruction to ventricular outflow have been reported in patients with Friedreich’s ataxia who have cardiac involvement. Outflow tract gradients on both sides of the heart are well recognized, and Thoren has commented on the frequency of systolic murmurs, which tend to disappear as patients become older and therefore may not be recognized by cardiologists or neurologists dealing only with adult patients. Angiocardiographic studies have shown appearances very similar to those found in hypertrophic obstructive cardiomyopathy. A large body of pathological evidence is not available, but histological examination of 16 hearts by Hewer showed considerable muscle hypertrophy with large and bizarre muscle fibers somewhat reminiscent of hypertrophic obstructive cardiomyopathy and often severe interstitial fibrosis. Evidence is so far not available on the distribution and orientation of the muscle fibers and on electron microscope studies. A striking difference, however, was the severe though not widespread narrowing of small coronary arteries, which was considered to be secondary to the cardiac muscle disease rather than a primary condition. This difference, together with the absence of any evidence of similar neuromuscular disease in patients with hypertrophic cardiomyopathy, or of the development of neuromuscular disease with age in the same condition, suggests that the two are probably separate disorders, in spite of interesting similarities. However, it is interesting to postulate a possible common factor in the form of excessive sympathetic discharge or inappropriate reaction of the heart muscle to normal sympathetic discharge.

The Natural History of Hypertrophic Cardiomyopathy

The natural history of hypertrophic cardiomyopathy is, I believe, largely determined by the stiffness of the left ventricle and the filling problems, and the clinical course tends to be related mainly to the level of the left ventricular end-diastolic pressure, particularly on effort. Most patients appear to have some degree of obstruction to left ventricular outflow tract, either persistently or on provocation, at some time during their lifetime, but there is no doubt that others in whom evidence of outflow tract obstruction disappears may develop severe heart failure, often associated with atrial fibrillation and embolism. This course of the disease however does not appear to occur in more than approximately 10% of patients.

Our original study of the natural history revealed that most patients maintained a stable course, but that a minority of patients tended either progressively to deteriorate or to apparently improve symptomatically. Sudden death is a well recognized complication and in our experience appears to be slightly more probable in patients with a particularly high left ventricular end-diastolic pressure and a short history of symptoms of increasing severity. Studies by my colleague Dr. Oakley in our patients have suggested that the prognosis may be particularly unfavorable in children in whom there may be widespread disease and extensive generalized hypertrophy. Our study by Swann and others showed that symptoms and their deterioration were related to the level of left ventricular end-diastolic pressure, as might be expected. There was no relationship between either severity of symptoms or tendency to deterioration and the left ventricular systolic gradient, suggesting that this is a
less important feature. A more recent study of our material\textsuperscript{21} based on 120 patients who were followed for an average of four and one half years revealed that familial or suspected familial disease was present in 39, the commonest mode of death being sudden, which occurred in 19 patients. Young males with a familial history seemed to be more prone to die suddenly than other patients. The estimated mortality was 15% at five years, and 35% at ten years, giving an annual mortality rate of 3.5% (fig. 6). The average age of onset of symptoms was 28 years and the average duration of symptoms before death was nine years. In many patients, however, deterioration was slow, though the development of atrial fibrillation was associated with a striking increase in symptoms. It is probable that the developmental myocardial abnormality is present from birth and that the detection of the murmur usually precedes symptoms (fig. 7). In this series it was noted that treatment with beta-adrenergic blockade did not prevent sudden death, though most of the patients had been treated with doses that would now be regarded as less than optimal.\textsuperscript{19}

A multicenter study by Shah et al.\textsuperscript{22} into the natural history of hypertrophic obstructive cardiomyopathy, which included much of our case material, was concerned with the course of 190 patients who had proven left ventricular outflow tract obstruction. This series excluded all patients without outflow tract obstruction, and thus, according to our views, would have excluded perhaps 10% of patients. The incidence of severe symptoms increased with each decade, being 9% for the first decade, and 70% for the sixth to eighth decades. Fifteen of 58 patients who underwent myotomy of the left ventricular outflow tract died at or after operation. Thirty-one of the remaining 172 patients died of the disease, giving a mortality of 18% for the 5.2 years of average follow-up and an annual mortality of 3.5%. This figure was identical to our findings\textsuperscript{21} in a series which included patients both with and without outflow tract obstruction. Twenty-six of 31 deaths were sudden. Seven percent of the deaths were in patients who had been treated surgically; 18% of the patients dying were being treated with a beta blockade drug, and 16% without any treatment died.

These figures would suggest a more favorable influence of surgical treatment on prognosis than that of beta-adrenergic blockade. It is possible that resection of the outflow tract muscle might in some way slow down the progress of the disease or diminish abnormal contraction and relaxation and thus the development of further hypertrophy. However, the figures cannot be taken entirely at face value since patients without outflow tract obstruction who may have had more serious disease were excluded from the series, giving a bias in favor of surgery.

Undoubtedly sudden death is the most important feature of the natural history in this disease as it can be totally unexpected and there are few clues as to its imminence. Sudden death is well recognized in

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure6.png}
\caption{Figure 6}
\end{figure}

\textit{Duration of symptoms, follow-up and cause of death in 30 patients. SD (sudden death); PO = Postoperative Death; CCF = Congestive Cardiac Failure. IEND = Infective Endocarditis. (Reproduced from Hardarson et al.,\textsuperscript{24} by permission of the Editor of The Lancet.)}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure7.png}
\caption{Figure 7}
\end{figure}

\textit{The suggested natural history of hypertrophic obstructive cardiomyopathy. The vertical axis indicates the New York Heart Association Functional Classes of Disability. It is assumed that the abnormality of myocardial development is present at birth, and it is known that a murmur usually precedes symptoms. The average age of onset of symptoms in the series was 28 years and the average duration of symptoms before death, nine years. The condition of many patients deteriorated only slowly, the minority developing atrial fibrillation which usually produced striking increase in symptoms. Sudden death may occur in any age. Abbreviations: SOB = Dypnea; SD = Sudden Death; CCF = Congestive Cardiac Failure; AF = Atrial Fibrillation. (Reproduced from Hardarson et al.,\textsuperscript{21} by permission of the Editor of The Lancet.)}
children with the disease. Death in 17% of 102 children who died suddenly was due to nonobstructive or obstructive cardiomyopathy (E. Lambert, personal communication, 1973).

Progressive Loss of Outflow Tract Obstruction

The progressive disappearance of outflow tract obstruction appears to be associated with progressive advance of the disease. Thus the loss of the outflow tract obstructive murmur has been associated in our experience with progressive dyspnea and the development of heart failure.\(^1\) It appears likely that in the earlier stages of the disease, and throughout the lifetime of many patients, systolic function of the left ventricle remains good though ill-coordinated. Damage to left ventricular muscle, by reducing contractile power, diminishes the force of left ventricular contraction and thus reduces the outflow tract obstruction. This was well documented in a patient whom I treated in whom the signs of outflow tract obstruction disappeared completely following a large anteroseptal infarct produced by dissection of the left anterior descending coronary artery. In addition to the loss of signs of outflow tract obstruction, angina disappeared and the echocardiogram no longer showed the appearances of outflow tract obstruction.

In a recent report\(^2\) myocardium obtained at operation or necropsy from 20 patients (11 with obstructive and nine with nonobstructive disease) was studied by light and electron microscopy. All the muscle specimens showed the characteristic greatly hypertrophied, bizarrely-shaped, and abnormally oriented cardiac muscle cells in the septum. In patients who had obstruction these abnormalities were either absent or only rarely found in tissue from the left ventricular apex, posterior wall, or right ventricle. By contrast, many areas of abnormal cells were present in both the left ventricular free wall and right ventricle in seven of the nine patients without obstruction who were symptomatic. The authors concluded that the characteristic cellular abnormalities are always present in the septum but that the more extensive involvement of the free walls of ventricles is limited to patients without obstruction. These findings would certainly harmonize with our views that widespread disease with a poor prognosis may be found in the absence of any obstructive element. It seems likely that the pattern of the disease is determined largely by the extent, distribution, and progression of the specific myocardial lesions.

Progressive deterioration leading to heart failure is caused by a number of factors: notably, the reduced left ventricular filling time and increased left ventricular filling resistance, and tachycardia, which limits filling time, causes further increase in left ventricular end-diastolic pressure and may thus precipitate heart failure. The development of atrial fibrillation, with consequent loss of atrial drive, together with increasing hypertrophy and extension of the disease, completes the picture of deterioration leading to death in heart failure. It is likely also that these factors contribute to, or may be the cause of sudden death when sudden limitation of filling capacity causes a precipitous fall in cardiac output and coronary blood flow with consequent ventricular fibrillation.

Prospects and Predictions for Hypertrophic Cardiomyopathy

In the light of the known factors and numerous speculations, it is now appropriate to attempt to predict the paths of investigation that would be desirable for the further elucidation of this disease over the coming years.

First, a follow-up study of patients’ relatives to determine the incidence of the disease and its patterns of progression would clearly be of great value. An increase in the ratio of thickness of ventricular septum to posterior wall in patients with hypertrophic cardiomyopathy has been demonstrated in a limited number of patients.\(^2\) If this initial study proves to have validity in larger numbers, then serial echocardiographic examinations would provide a useful, harmless, and subtle way of diagnosing presymptomatic stages of the disease and following its development in individual patients.

Second, serial examination of patients by noninvasive techniques such as echocardiography will be needed to determine the effect of long term beta-adrenergic blockade on the incidence of sudden death. The persuasive evidence obtained by acute observations and the theoretical considerations involved suggest a beneficial role for beta-adrenergic blockade and indicated that further evaluation of the place of long-term, high dosage regimes is needed.

Third, efforts should be directed to a study of the catecholamine content of the specific lesions in the myocardium in hypertrophic cardiomyopathy using new and refined techniques of fluorescent staining. Attempts should be made to determine whether conditions such as Pompe’s disease and Friedreich’s ataxia that produce clinical hemodynamic and gross morphological abnormalities similar to hypertrophic cardiomyopathy also show the characteristic myocardial ultrastructural lesions. Further studies of catecholamine function and production in conditions in which abnormality of catecholamine metabolism or response may be a common factor are needed.

Finally it should be possible to attempt to create an experimental model of the disease by determining the effect of abnormal orientations of developing cardiac
CARDIOMYOPATHIES

In my view it is unlikely that much further study of the exact dynamics of outflow tract obstruction and mitral regurgitation will yield significant additional basic information regarding the disease. The hemodynamics, clinical features, and prognosis have already been reasonably accurately delineated. Knowledge of the cause of the disease, its relationship to other cardiac and noncardiac conditions, and an effective method of treatment are urgently needed.

Congestive Cardiomyopathy

I turn now to the enigma of congestive cardiomyopathy. This is a multifaceted syndrome characterized by isolated cardiomegaly with dilated ventricles, heart failure, and more extensive hypertrophy than would be expected from the degree of dilatation. It is likely that there are many causes and the definition covers not a single disease but a syndrome that is a final common path of many differing conditions that insult the ventricular myocardium.

Insults that deserve particular study are those of alcohol, pregnancy and the puerperium, systemic hypertension, and infections, probably of viral nature. These four phenomena may be regarded as "risk factors" if not actual causes, for it is probable that in many instances it is the combination of more than one factor that produces the devastating damage to the myocardium.

It is true that other myocardial diseases can produce the clinical and pathological final common path known as congestive cardiomyopathy. These are conditions such as endocardial fibroelastosis, Chagas' disease, and many infiltrative diseases of the myocardium or granulomatous disorders. There are also connective tissue disorders such as diffuse systemic sclerosis that may involve the myocardium.

I shall not consider alcohol further as it is well known that excessive amounts can produce a syndrome of severe congestive heart failure which is not infrequently fatal and which tends to improve when alcohol is discontinued and to recur when drinking is recommenced. It is likely, however, that some factor other than ingestion of alcohol is implicated since not every subject who takes large quantities of alcohol develops alcoholic cardiomyopathy. Probably individual differences and susceptibilities, and perhaps the presence of other risk factors, are important.

It has been suggested that systemic hypertension may be an important cause of congestive cardiomyopathy. The initial high systemic blood pressure and cardiac output may be succeeded by reduction in the cardiac output as a result of the high peripheral vascular resistance and resultant left ventricular systolic afterload.25 It is true that hypertension and cardiomyopathy may coexist in the same population, and Brockington and Eddington26 have argued persuasively that congestive cardiomyopathy might be the result of an unusual response of the left ventricle to the persistent afterload. While hypertension may well be a factor in some patients, or even a cause in a few, it seems improbable that it is a major factor in the majority since incidence of hypertension is uncommon and in our experience occurred in only approximately 25% of our patients, and in a number of these was probably a reaction to the severe heart failure.1

One of the outstanding problems of the present time is the possible connection between infective myocarditis produced by viruses on the one hand and established congestive cardiomyopathy on the other. There is remarkably little data on the transition from acute myocarditis to chronic congestive cardiomyopathy and almost no evidence to implicate a virus infection in patients with established congestive cardiomyopathy. Nevertheless, such evidence as there is may be important. Somerville27 described the transition from an acute pyrexial illness with involvement of the myocardium to a chronic state of heart failure consistent with congestive cardiomyopathy in three patients. Bengtsson28 described the presence of cardiac abnormalities in 30% of 200 patients five years after acute myocarditis. Obeyesekere and Herman28 described the development of congestive cardiomyopathy after arbovirus infection in Ceylon in ten patients. So far there is minimal direct evidence of the presence of viruses or the hallmarks of virus myocardial disease in patients with congestive cardiomyopathy, but Kawai29 demonstrated an increased incidence of complement-fixing antibodies to various viruses, including poliomyelitis, coxsackie-B, and influenza, in heart muscle cells of patients with idiopathic cardiomyopathy, as compared with controls. He also demonstrated positive fluorescence for adeno-virus antigen in the nuclei of myocardial cells from a biopsy from right ventricular myocardium in patients with cardiomyopathy.

Immunoglobulin-binding in the heart muscle cells of patients with congestive cardiomyopathy has been described30 but this is not necessarily of etiological significance and might be the result of an infective process. The fact that viruses have not so far been implicated directly in the causation of congestive cardiomyopathy in any way denies this possibility, and with better methods of virus detection and improving techniques of cardiac biopsy, it should be possible to answer this important question which assumes even greater relevance now that we are on the threshold of development of antiviral chemotherapy.

I have long been intrigued by the excess of dilata-
tion over hypertrophy in congestive cardiomyopathy and have wondered if in some way the normal mechanisms in hypertrophy that compensate for myocardial weakness have been frustrated in congestive cardiomyopathy. The dilatation of the left ventricle is diffuse, symmetrical, and akinetic, and thus differs strikingly from the dyskinetic ventricular pattern so commonly seen in occlusive coronary artery disease. This difference harmonizes with the absence of significant coronary artery disease in patients with congestive cardiomyopathy. It is possible that the agents that damage the myocardium interfere with contractile function by preventing calcium-binding by troponin and that the deficient contractile function that follows results in ventricular dilatation, increased wall tension, and failure of the RNA-DNA response that is needed to produce hypertrophy. This is sheer speculation, but our studies of the relation of hypertrophy to prognosis in congestive cardiomyopathy suggest that patients with the most hypertrophy appear to have the best prognosis. Long-term survival was unusual when the end-diastolic volume rose to over two and a quarter times the maximum normal or when the ejection fraction was less than 10%, compared to over 60% of the control value.

The failure to discover any characteristic features on ultrastructural studies or the myocardium in congestive cardiomyopathy suggests that the appearances may represent little more than a graveyard of dead tissue without revealing the cause of death and that ultrastructure studies are of only limited value. The investigation of the tombstones in a graveyard, however detailed, will not yield clues to the cause of death of the bodies beneath.

It therefore becomes necessary to look beyond the boundaries of structure and ultrastructure to the finer processes of myocardial chemistry and cellular biology. Studies of subcellular organelle enzymes and the functions of lysosomes, which, on being damaged, rupture and release enzymes that may digest cells, have been started at the Royal Postgraduate Medical School by my colleagues C. M. Oakley and T. Peters.

Prospects and Predictions for Congestive Cardiomyopathy

The problems are in many ways much greater than for hypertrophic cardiomyopathy because we are not dealing with a discrete disease entity but a multifactorial syndrome producing a final common path toward irreversible myocardial damage. The most fruitful approach is likely to come from improved techniques of cardiac biopsy that permit safe and repeated studies of myocardial function to be made, and from improved studies of cellular biology with examination of enzyme systems and search for viruses and their products.

It should be possible to create an animal model that satisfies the hemodynamic and clinical characteristics of congestive cardiomyopathy by the administration of such infective or toxic agents that might possibly be causally related in man.

Accurate long-term follow-up studies of cases of known acute myocarditis to detect chronic cardiac damage are essential.

Epidemiological studies of congestive cardiomyopathy should be undertaken to determine whether other factors, as yet unsuspected, may be involved. General agreement on the diagnostic criteria for congestive cardiomyopathy is vital and multicenter studies could be of great value, provided uniformity of case material and rigid criteria of diagnosis are insisted upon. Here the Scientific Council on Cardiomyopathies of the International Society of Cardiology might be of crucial importance.

At the present time the prognosis for severe congestive cardiomyopathy is so bleak and treatment so unsatisfactory that cardiac transplantation may be considered in desperate cases.

Conclusions

I have not attempted to be comprehensive and to cover all aspects of the cardiomyopathies. Rather, I have selected those aspects and features that I believe to be of major import and that require further study in the future and I have not hesitated to be provocative with hypothesis. As in so many areas of medicine, the study of the cardiomyopathies requires the integrated efforts of research workers in many disciplines — clinical, pathological, biochemical, virological, immunological, epidemiological, and possibly others not as yet considered. The intellectual challenge and stimulation provided by this fascinating and taunting group of diseases may be blunted by the emotional frustration arising from the unfortunate prognosis and the limitations of treatment. But nevertheless we should never lose our scientific curiosity, which has been compared to "that direct incontinence of the spirit which has a pleasure in it like wrestling with a fine woman."

Acknowledgment

I am deeply sensible of the honor done to me by the American Heart Association in having asked me to deliver the lecture upon which this paper is based.

It is a pleasure to acknowledge the work, originality, and stimulating ideas of many colleagues on both sides of the Atlantic and I am profoundly grateful for the help that they have given me.

References

2. Tearn RD: Asymmetrical Hypertrophy of the Heart in Young Adults. Br Heart J 20: 1, 1958

Circulation, Volume 50, August 1974
17. GACH JV, ANDRIANJ M, FRANK D: Hypertrophic Obstructive Cardiomyopathy in Friedreich’s Ataxia. Am J Cardiol 27: 436, 1971
Prospects and Predictions for the Cardiomyopathies

J. F. GOODWIN

Circulation. 1974;50:210-219
doi: 10.1161/01.CIR.50.2.210

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1974 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/50/2/210.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/