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The Challenge of Cardiomyopathy

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The combined clinical and pathophysiologic characteristics and diagnostic features as well as current concepts of pathogenesis, therapy and prevention of the principal forms of cardiomyopathy are reviewed. These include hypertrophic cardiomyopathy, dilated cardiomyopathy, restrictive cardiomyopathy and specific cardiac muscle disease. Emphasis is placed on recent developments and unresolved questions requiring application of newer techniques of molecular biology and genetics and adult myocyte culturing.

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"D'où venons nous? Que sommes nous? Où allons nous?" Thus, Paul Gauguin entitled his monumental canvas of 1897, which addresses the human condition and life cycle. Since then, biomedical science has elucidated much of this cycle and also has prolonged it for many individuals. If we look at the natural history of individual diseases, the same may be said for many diseases of heart muscle. We know a great deal more about their origins and are able to recognize them earlier and more widely. Their life cycle has been extended, and we see the late stages with increasing frequency.

Some afflictions of the heart have decreased in prevalence and importance, at least in the more developed countries, partly because of effective prevention or treatment, or both, and partly for reasons that are unclear. Among these are syphilis, rheumatic fever, tuberculosis and malignant hypertension. On the other hand, diseases of heart muscle appear to be more prevalent either because they have increased in incidence or because they are being recognized more frequently; they have become more prominent as causes of morbidity, disability and mortality. This observation holds for a wide range of presentations and manifestations, such as decreased tolerance of activity, congestive heart failure, arrhythmias, conduction disturbances, chest pain and sudden death.

This article will not review present knowledge and understanding of the cardiomyopathies in detail; many recent comprehensive reviews are available (1–12). Rather, we shall emphasize recent contributions, try to present the highlights of our knowledge in perspective, address gaps of knowledge and understanding and raise questions to be addressed in the future.

Historical Perspective

Disease of heart muscle, as distinct from valvular, coronary, pericardial or congenital heart disease, was recognized as early as 1891 by Krehl (13) in Germany, and reemphasized in 1901 by Josserand and Gallavardin (14) in France and in

This article is part of a series of articles celebrating the 40th anniversary of the American College of Cardiology. The series attempts to set the stage for the future by describing current state of the art management of selected major cardiovascular problems and the basic knowledge that will provide directions for advances in diagnosis and therapy.

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1933 by Christian (15) in the United States. However, it came into prominence and wide recognition only in the second half of this century, thanks largely to the contributions by Mattingly (16), who reintroduced the term "primary myocardial disease," and Harvey et al. (17) in the United States, and by Brigden (18), who introduced the term cardiomyopathy, and Goodwin and associates (19) in Great Britain. Originally, the designation "primary" signified that the disease predominantly affected the myocardium. Later, "primary" came to designate idiopathic afflictions of heart muscle, as distinguished from diseases of other organ systems that affect the heart secondarily.

Classification of cardiomyopathy. Initially, primary myocardial disease was considered a diagnosis of exclusion, that is, a diagnosis to be made after other etiologies had been ruled out. Gradually, it became recognized that there were characteristic albeit nonspecific features that permitted recognition of primary myocardial disease on its own merits. Furthermore, it became evident that there were different groupings of structural and physiologic characteristics, leading to a functional classification first introduced by Goodwin (19) and, in 1968, adopted by the World Health Organization (WHO) (20). This classification distinguished hypertrophic cardiomyopathy with or without obstruction, initially known in the United States as idiopathic hypertrophic subaortic stenosis (IHSS), from congestive cardiomyopathy and restrictive cardiomyopathy. In a later modification, the WHO (21) classification was altered in that "congestive cardiomyopathy" was relabeled "dilated cardiomyopathy", and cases in which a specific etiology or associated systemic disease could be identified were now assigned to a new category of "specific heart muscle disease." Furthermore, two new categories, "obliterative cardiomyopathy" and "indeterminate cardiomyopathy" were added.

Heart muscle disease secondary to specific causes or disease entities (for example, thiamine deficiency, hemochromatosis, amyloidosis, muscular dystrophy) according to the WHO definition are no longer included among the cardiomyopathies. However, the similar clinical presentations and therapeutic problems have led to widespread continuation of the use of the term cardiomyopathy for such cases, especially the frequently encountered entity of congestive heart failure secondary to chronic ischemic heart disease, generally referred to as "ischemic cardiomyopathy." The pragmatic advantage to the clinician of continuing to include congestive heart failure associated with specific heart muscle disease under the concept of dilated cardiomyopathy has been previously discussed in detail (5).

Pathogenetic mechanisms. The original concept that most idiopathic cardiomyopathies were attributable to a specific cause, if one but searched long enough and awaited the results of further research, has had to be discarded. More than 75 specific heart muscle diseases that may manifest as dilated cardiomyopathy have been described (5,22), but these disorders share common clinical, functional and pathologic manifestations. Moreover, experimental models of heart failure have shown a good deal of communality and overlap in the characteristics of individual forms of cardiomyopathy or specific heart muscle disease. Therefore, the concept of cardiomyopathy as a pluricausal or multifactorial disease has gained increasing acceptance (2,5,23). The principal pathogenetic mechanisms under current consideration include genetic factors, metabolic disturbances, hormonal imbalances, toxins, calcium overload, altered vascular reactivity, hypoxia, free radicals, infection and immune/autoimmune processes.

Incidence and Prevalence of Cardiomyopathy

In developed countries, the annual incidence of cardiomyopathy ranges from 0.7 to 7.5 cases per 100,000 population (24), and the prevalence in England has been reported as 8,317 cases per 100,000 population (25). At least 0.7% of cardiac deaths in the United States have been attributed to cardiomyopathy (24); the male cardiomyopathy mortality is twice that of female, and blacks have more than twice the mortality rate of whites. It is generally believed that dilated cardiomyopathy constitutes >90% of all cardiomyopathies encountered.

In less developed countries, especially in the tropics, cardiomyopathies are most prevalent and also constitute a greater if not dominant fraction of heart disease (24). This greater prevalence is largely in the form of dilated cardiomyopathy and to some extent of restrictive cardiomyopathy; it has been attributed variously to genetic factors, nutritional deficiency, infection including Chagas' disease, physical stress, untreated hypertension, endomyocardial fibrosis and toxins such as ethanol (26).

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy has held the fascination of cardiologists despite its rarity because of its dramatic aberrations of geometry and function and its importance as a cause of disability and death in young, otherwise healthy adults. Over the past 3 decades, our appreciation of the pleomorphic, geometric and hemodynamic manifestations of hypertrophic cardiomyopathy has greatly increased because of an enlarging body of natural history data and technologic advances in cardiac imaging. However, major gaps in knowledge of the etiology and pathophysiology remain. This discussion will first present the historical perspective of the initial disparate evolution and more recent convergence of concepts regarding pathogenic mechanisms in hypertrophic cardiomyopathy. From this perspective, we will highlight major unanswered issues that require attention if further strides are to be made in the treatment of symptomatic patients, prevention of premature sudden death and, ulti-

mately, alteration of natural history and the regression of hypertrophy in this cardiomyopathy.

Historical Perspective

Early studies. Hypertrophic cardiomyopathy has been recognized in clinical practice for only 3 decades. However, Brigden (27) recently emphasized that isolated cardiac hypertrophy with an element of outflow tract stenosis was identified by pathologists in the 19th century and clearly described by Schminke as "Muskulöse Conusstenosen" in 1907. Both its familial nature and association with sudden death were raised by Evans' description (28) of a kindred with unexplained hypertrophy in 1949. However, this disorder first came to widespread international attention as an entity that could mimic valvular stenosis due to functional obstruction by hypertrophied muscle with the publication of Brock's case report (29) in 1957 and Teare's description (30) in 1958 of the necropsy finding of unexplained septal hypertrophy in seven young adult victims of sudden death. During the 1960s, investigators in the United States, particularly at the National Institutes of Health, focused on the identification and detailed assessment of those patients with the obstructive form of the disease. In addition to confirming the familial transmission of this entity, elegant hemodynamic studies elucidated the physiology of this subset of patients whose hallmark was the presence of a dynamic systolic murmur and pressure gradient consistent with the presence of functional obstruction to left ventricular outflow (31,32). The anatomic basis of the dynamic outflow gradient was suggested by angiographic studies and shown by M-mode and later two-dimensional echocardiography to depend on narrowing of the left ventricular outflow tract by asymmetric septal hypertrophy and systolic anterior movement and apposition of the mitral valve leaflet to the septum (33).

This concept of hypertrophic cardiomyopathy as a disorder whose fundamental characteristics were the presence of asymmetric septal hypertrophy and dynamic outflow tract obstruction was supported by the clinical improvement of symptomatic patients with interventions aimed at reducing the dynamic outflow gradient, including the use of negative inotropic agents such as propranolol and surgical ablation of the gradient using the myotomy-myectomy procedure pioneered by Morrow et al. (34). Necropsy studies in these patients demonstrated the consistent finding of disorganization and malalignment of the myofibrils (myofibrillar disarray), which is not unique to hypertrophic cardiomyopathy but is clearly more extensive in this disorder than in secondary hypertrophy from pressure overload or congenital heart disorders (35).

Obstructive versus nonobstructive form. During this exciting period of discovery and description, it was clearly recognized that not all patients had severe outflow tract pressure gradients and that abnormalities of diastolic function were common (36). Nonetheless, the emphasis on regional septal hypertrophy and its relation to the systolic murmur and gradient led to a profusion of terms such as "idiopathic hypertrophic subaortic stenosis" and "muscular subaortic stenosis." Furthermore, particularly in the United States, the widespread interest in the subset of patients with "IHSS" was accompanied by their ease of recognition by physical examination and office-based echocardiography. It can be argued that these combined factors resulted in the widespread perception that hypertrophic cardiomyopathy could only be identified in patients with the clinical signs of rest or provokable outflow tract gradients who had documented asymmetric septal hypertrophy and systolic anterior mitral valve motion. As a consequence, during the "IHSS" era, patients with other phenotypic manifestations, nonobstructive physiology and older patients with the confounding presence of mild hypertension were outside the mainstream of clinical recognition and study.

Clinical investigations. In parallel with these lines of investigation, there was the acquisition of natural history data, identification of kindreds and clinical investigation of patients with hypertrophic cardiomyopathy drawn from somewhat different patient referral populations in the United Kingdom. These observations led to the insights that the presence of a systolic murmur indicative of a left ventricular outflow gradient was not an invariable feature of the disease within kinships of patients, or in the natural history of an individual followed from adolescence through adulthood (2,37,38). In individuals who presented with the dramatic signs of outflow obstruction in young adulthood, clinical deterioration in middle age was frequently associated with the disappearance of the dynamic systolic murmur and the development of physiologic features resembling those of restrictive cardiomyopathy. Second, it became apparent that, although the extent of septal hypertrophy and duration of mitral leaflet-septal apposition correlate well with the magnitude of the systolic gradient, cardiac morphology does not correlate well with either symptoms or natural history. Severe symptoms of angina, pulmonary congestion and syncope occur in patients with either the obstructive or the nonobstructive forms of the disease, and many but not all investigators observed that there appears to be little relation between the magnitude of the systolic gradient and the severity of symptoms or improvement in functional status with pharmacologic agents (39–41).

Echocardiographic contributions to diagnosis of morphologic forms. Two-dimensional cineangiographic studies and the ability to look at cardiac geometry in a new way with two-dimensional echocardiography revealed that patients with hypertrophic cardiomyopathy can exhibit unexplained hypertrophy in regions other than the upper portion of the ventricular septum, including the midportion of the left ventricle, the apex, the lower portion of the septum as well as severe concentric hypertrophy (42–44). Furthermore, this

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variability in cardiac geometry can occur not only in isolated individual patients but also within kindreds (45). Two morphologic forms of hypertrophic cardiomyopathy merit particular attention: apical hypertrophy and midventricular hypertrophy. These atypical forms are of interest not because of their prevalence but because they underscore the fact that our perception of hypertrophic cardiomyopathy has been powerfully shaped by the capabilities and limitations of the tools available for the study of patients. Both of these forms of hypertrophic cardiomyopathy are associated with nonspecific physical findings, escape detection by M-mode echocardiography and have come to attention with two-dimensional imaging with use of either contrast ventriculography or two-dimensional echocardiography.

In the late 1970s, Japanese investigators reported on cohorts of patients with severe apical hypertrophy identified by invasive contrast ventriculography who lacked signs of outflow tract obstruction and often came to clinical attention because of bizarre electrocardiographic (ECG) findings of severe left ventricular hypertrophy with giant negative T waves (46). This expression of hypertrophic cardiomyopathy is especially prevalent in Japan but has now been identified with use of two-dimensional echocardiography in other genetic and geographic populations and within kindreds with other phenotypic patterns of hypertrophy. A second subset of patients that did not receive attention in the era of the identification of hypertrophic cardiomyopathy with M-mode echocardiography is that of patients with severe midventricular hypertrophy below the level of the outflow tract at the level of the papillary muscles. At cardiac catheterization, such patients can be shown to have midventricular "obstruction" with a gradient between the left ventricular apical region and the remainder of the chamber due to the generation of markedly elevated levels of left ventricular systolic pressure by an isometric contraction in a discrete apical cavity (42,47). In our experience and that of Wigle et al. (42), some patients show progression to an appearance of a noncontractile apical aneurysm and apical thrombus formation can occur. In such patients who have documentation of normal epicardial coronary arteries, the responsible mechanism may be the repetitive generation of high levels of isometric pressure, which ultimately results in episodes of ischemic injury and necrosis.

The true frequency of these different phenotypes of hypertrophic cardiomyopathy is difficult to ascertain. Referral centers with expertise in the medical and surgical management of the obstructive form of the disease report a predominance of asymmetric septal hypertrophy, whereas this morphologic expression appears to occur in the minority at centers that accrue a different spectrum of patients. Nonetheless, these lines of investigation and observation from different referral populations and different parts of the world have converged to a consensus position that the central morphologic feature of hypertrophic cardiomyopathy is the presence of a nondilated hypertrophied left ventricle detected in the absence of a primary illness that could cause hypertrophy (48,49).

Evolving Concepts and New Questions: Role of Ischemia

Myocardial ischemia. The importance of ischemia in hypertrophic cardiomyopathy is an area of increasing interest and clinical investigation. Angina pectoris is a cardinal symptom of hypertrophic cardiomyopathy and can occur in all morphologic forms of the disease. There is substantial evidence that the symptom of angina pectoris is related to myocardial ischemia in these patients. Similar to observations in patients with secondary pressure overload hypertrophy (50), interventions such as pacing tachycardia and exercise can provoke chest pain in association with elevation of left ventricular filling pressure, myocardial lactate production and the development of reversible perfusion defects detectable by thallium imaging (51–53). In addition, autopsy studies of patients with hypertrophic cardiomyopathy and patent epicardial coronary arteries have demonstrated the presence of fibrous tissue that varies from a patchy subendocardial distribution to large transmural scars (49). These observations strongly support a role of repetitive ischemic injury and necrosis in the symptomatology and natural history of the disease.

Mechanisms for ischemia. Several mechanisms are likely to be responsible for myocardial ischemia in hypertrophic cardiomyopathy. First, abnormal narrowing of the small intramural coronary arteries due to intimal and medial thickening in association with regions of myocardial fibrosis occurs in the majority of patients studied at autopsy (54). The role of this form of small vessel disease as a cause of ischemia is not yet clear. In addition, patients with hypertrophic cardiomyopathy may have impairment of coronary vascular reserve and susceptibility to develop subendocardial ischemia that is characteristic of advanced secondary hypertrophy and related to a reduced capillary density (55). Third, the exacerbation of impaired relaxation and further elevation of left ventricular diastolic pressure during tachycardia or exercise in patients with hypertrophic cardiomyopathy and secondary hypertrophy may itself further limit coronary perfusion, particularly in the subendocardium. This hypothesis is supported by the observation of Cannon et al. (51) that coronary blood flow actually decreases during pacing-induced angina in some of these patients. Fourth, there is experimental evidence (56) in models of pressure overload hypertrophy that myocardial hypoxia is accompanied by an impaired capacity to recruit anaerobic glycolysis. Preliminary studies (57) in patients with hypertrophic cardiomyopathy using positron emission tomography are consistent with a mismatch between impaired myocardial per-

fusion and utilization of glucose substrate, but further studies are needed to address this issue.

Significance of the Systolic Pressure Gradient

The concept of outflow tract obstruction. The concept of left ventricular outflow obstruction has been criticized by investigators (58,59) who have argued that intraventricular gradients are related to gradients between rapidly and slowly emptying regions in association with cavity obliteration. Murgo et al. (60) also have challenged this notion on the basis of studies of aortic flow velocity, which suggested that patterns of flow were similar in patients with and without an outflow gradient and that both groups manifested the very rapid ejection of most of the left ventricular stroke volume very early in systole. However, multiple recent studies using cineangiographic, echocardiographic and Doppler flow methods lend support to the concept of "obstruction," defined as ventricular emptying that occurs in the presence of a pressure gradient across the outflow tract. As recently summarized by Wigle (61) and Maron and Epstein (62), multiple studies indicate that the onset of septal-mitral leaflet contact correlates with both the development of the systolic gradient and the abrupt deceleration of aortic flow, whereas the time of onset and duration of contact predict the magnitude of the gradient, the proportion of ventricular emptying that occurs in the presence of the gradient, and the prolongation of left ventricular ejection time. Furthermore, there are substantial data to support the hypothesis that septal-mitral leaflet contact occurs because of a Venturi effect of very rapid velocity of flow across the narrowed outflow tract in early systole (61). However, we support the concerns of many investigators in the field that the amount of energy that has been expended in the controversy of "proving" or "disproving" that obstruction exists has not yielded proportionate insight into our understanding of the ways in which the systolic gradient may contribute to symptoms or the natural history of the disease.

Hypothesis of repetitive cycles of increased wall stress and oxygen demand leading to ischemia, necrosis and fibrosis. A different viewpoint is that the repetitive development of large systolic pressure gradients may be deleterious as a mechanical stimulus for further hypertrophy and because it is energy-costly in a hypertrophied ventricle with impaired coronary vascular reserve. This concept is supported by the observation that patients with left ventricular outflow obstruction exhibit higher levels of myocardial oxygen consumption at rest and during pacing tachycardia in comparison with patients without outflow obstruction (63). From this perspective, it is possible to have a unifying hypothesis that addresses the fact that symptoms of angina and exertional dyspnea and the development of myocardial fibrosis can occur in patients with classic asymmetric septal hypertrophy and outflow gradients, midventricular obstruction and diffuse hypertrophy with cavity obliteration. In each of these settings, the repetitive development of high levels of left ventricular systolic pressure may trigger a dangerous cycle of increased regional or global systolic wall stress and myocardial oxygen demand that provokes the development of ischemic injury, necrosis and fibrosis.

This hypothesis is consistent with the well established observation that many patients with a large rest outflow gradient improve symptomatically after myotomy-myectomy. This improvement may be related to the ablation of regional myocardium involved in a vicious cycle of high wall stress and ischemia as opposed to the relief of "obstructed" blood flow. The advent of new technologies that will permit the assessment of global and regional changes in both myocardial perfusion and metabolism provide an exciting opportunity to address this hypothesis.

Diastolic Function

Abnormalities of left ventricular relaxation. The last 2 decades have seen an explosion of international interest in diastolic function in hypertrophic cardiomyopathy and in secondary pressure overload hypertrophy. In both forms of hypertrophy, clinical congestive heart failure is a major cause of disability despite the preservation of left ventricular systolic function. In both forms of hypertrophy, left ventricular diastolic pressure is usually elevated relative to a normal or diminutive diastolic volume consistent with decreased diastolic distensibility of the left ventricular chamber. Similar to secondary pressure overload hypertrophy (64), these findings are due in part to altered passive diastolic properties of the left ventricle related to both the extent of hypertrophy and changes in composition of the ventricle, including possible alterations in the collagen matrix and deposition of fibrous scars (65). In addition, the elevation of left ventricular filling pressure is in part related to changes in the rate and extent of left ventricular pressure decay, that is, left ventricular relaxation (66). In some patients, left ventricular relaxation is so aberrant that left ventricular pressure continues to decline sluggishly throughout diastole, instead of showing the usual pattern of decreasing rapidly to its nadir in early diastole at mitral valve opening (67).

The responsible mechanisms for impaired left ventricular diastolic function are as yet incompletely understood and include a slowing of force inactivation at the level of the myofibril related to abnormal calcium handling, abnormal patterns of electromechanical activation, regional dyssynchrony of the time course of contraction and relaxation and impaired relaxation due to ischemia. Many but not all patients also show a slowed rate of left atrial emptying and early left ventricular diastolic filling with an enhanced dependence on left atrial contraction (66–69). These patients usually have an elevated left atrial pressure, and thus the presence of impaired diastolic filling is striking because

elevation of left atrial pressure and the driving force across the mitral valve would otherwise tend to accelerate left ventricular filling.

Diastolic inflow obstruction of the left ventricle. The consistent finding of abnormal diastolic function in patients with the obstructive and nonobstructive forms of the disease has led to the hypothesis proposed by Goodwin (48) and others (66–69) that a major defect is diastolic "inflow obstruction" of the left ventricle. The elevation of diastolic pressure and the increased resistance to diastolic filling, which is especially important when the diastolic filling period is shortened by tachycardia, contribute to symptoms of pulmonary venous congestion and to easy fatigue and near syncope during exertion related to inadequate diastolic filling. Because of these abnormalities of diastolic function, the development of atrial fibrillation is a "double whammy" that results in both abbreviation of the time available for diastolic filling and the loss of atrial transport.

Implications for Therapy

Beta-blockers. For this reason, drugs such as beta-adrenergic blocking agents, which exert a primary myocardial effect of slowing relaxation and do not improve diastolic filling rates, may indirectly decrease dyspnea and increase exercise reserve through improved "diastolic function" by slowing the heart rate, lengthening the diastolic filling period and facilitating a greater extent of diastolic filling.

Calcium channel blockers. The calcium channel blocking agents, such as verapamil, nifedipine and diltiazem, have been studied extensively and have been reported to improve left ventricular relaxation and the rate and extent of left ventricular filling in patients with both the obstructive and nonobstructive forms of the disease (67,69,70). Despite intense clinical study, the mechanisms of action are controversial and may include alteration of loading, induction of increased sympathetic tone, reduction of regional asynchrony and relief of subendocardial ischemia (71,72). A controversial issue that has not yet been answered is whether these agents exert a direct myocardial effect on cytosolic calcium handling in patients with hypertrophic cardiomyopathy. The benefit tends to be greatest in patients with severe elevation of left ventricular end-diastolic pressure and impairment of relaxation and filling, but the effects of these agents on diastolic function are not uniform and precipitation of pulmonary edema can occur. Although improvement in diastolic function has also been observed with short-term administration of amiodarone, similar to that seen with calcium blockers, long-term therapy has been associated with the elevation of left heart filling pressures and no improvement in diastolic relaxation (73).

Side effects. Although calcium channel blockers have been an important addition to treatment options, these agents must be used with great caution because of their chronotropic side effects (bradycardia and isorhythmic dissociation with loss of atrial contraction with verapamil and reflex tachycardia with nifedipine) and the risk of excessive vasodilation and hypotension with both agents (74,75). Thus, the quest for the ideal lusitropic agent to reliably enhance left ventricular relaxation has not been fulfilled with available agents and merits further investigation by both academic research centers and the pharmaceutical industry.

The Dilemma of Sudden Death

Predictors of sudden death. Since the initial case reports, sudden cardiac death has been an ominous feature of hypertrophic cardiomyopathy distinct from its hemodynamic abnormalities. Similar to dilated cardiomyopathy, major unanswered problems are the ability to identify individual patients at high risk of sudden death and to define treatment strategies that reduce this risk. Although the overall annual mortality rate for patients studied at referral centers is estimated to be 2 to 3%, the risk of premature death is skewed by a high incidence of sudden cardiac death in children and young adults (39,49,76). In about 50% of patients, death occurs suddenly, is unexpected and can be the index presentation of hypertrophic cardiomyopathy. Ominous prognostic features for an increased risk of sudden death include young age (first 3 decades of life), documented syncope and a family history of sudden death (39). It is still controversial whether the extent of hypertrophy is an independent predictor of sudden death. Otherwise, it is not predicted by symptoms, functional limitation, hemodynamic abnormalities including the presence or absence of left ventricular outflow obstruction or rest ECG abnormalities (40,49).

Mechanisms. In this disorder, sudden cardiac death can probably occur from multiple mechanisms including hemodynamic deterioration, complete heart block, bradyarrhythmias and atrial tachycardia with concealed atrioventricular (AV) conduction. However, the predominant mechanism is probably the development of a sustained ventricular tachyarrhythmia. Although this condition has been documented only rarely as a cause of witnessed sudden death (77), several centers (78,79) have reported that asymptomatic episodes of ventricular tachycardia detected by ambulatory Holter ECG monitoring are predictive of an increased risk of sudden death in adults. In patients referred to the National Institutes of Health, a single episode of ventricular tachycardia during ambulatory monitoring was associated with an 8% risk of sudden death per year, compared with a 1% risk in patients without ventricular tachycardia (79). The mechanisms responsible for the initiation of ventricular tachycardia in these patients including the potential contribution of ischemia, are not known.

Prevention: role of beta-adrenergic blockers. Beta-adrenergic blocking agents have been used widely as an

antidote to reduce the risk of sudden death in both symptomatic adults and asymptomatic children and young adults in whom hypertrophic cardiomyopathy is detected incidentally by routine physical examination or screening echocardiography. The rationale for use of these drugs is bolstered by awareness of the potential role of ischemia in this disorder and the striking protective effect of beta-adrenergic blockers in reducing mortality in patients after myocardial infarction and possibly in patients with dilated cardiomyopathy. However, the effect of beta-blockers on the risk of sudden death in hypertrophic cardiomyopathy is not established. Propranolol administration does not appear to reduce the frequency of asymptomatic ventricular arrhythmias detected by Holter monitoring, and studies by McKenna et al. (80) in the United Kingdom have failed to demonstrate a protective effect of propranolol against sudden death. However, prospective, controlled, randomized trials have not been done to determine whether administration of beta-adrenergic blockers modifies the risk of sudden death in high risk young adults.

Other antiarrhythmic agents. There are also considerable controversy and few hard data regarding the efficacy of classic type I agents (quinidine, procainamide) in suppressing ventricular arrhythmias and preventing sudden death. Preliminary studies using amiodarone are promising. Available clinical trials that did not incorporate randomized controls suggest that amiodarone reduces the frequency of episodes of ventricular tachycardia detected by ambulatory monitoring and may be more effective than conventional agents including calcium channel blockers (81,82). However, there is a great concern about the long-term use of this agent in children and young adults because of the difficulty of evaluating efficacy, its proarrhythmic effects, its deleterious effects on left heart filling pressure and its uncommon but major side effects including pulmonary fibrosis. The potential role of invasive electrophysiologic testing to identify high risk patients and monitor efficacy of therapy and the use of implantable defibrillators in preventing sudden death also needs further study.

Unresolved: The Causes of Hypertrophic Cardiomyopathy

Familial transmission. There is some uncertainty regarding the true prevalence of familial versus sporadic forms of hypertrophic cardiomyopathy, which is influenced in part by the techniques used to detect occult disease (echocardiographic criteria for example) and the fact that morphologic expression of the disease may not be apparent until young adulthood. With these caveats, hypertrophic cardiomyopathy appears to be familial in nearly 60% of cases and sporadic in the remainder (83,84). A single pattern of inheritance is not characteristic, an observation that suggests that several genetic defects may contribute to the pool of patients now diagnosed as having hypertrophic cardiomyopathy. However, in about 75% of pedigrees with familial transmission, the pattern of inheritance is consistent with a single or linked gene defect of autosomal dominant transmission with variable penetrance and expression. Within pedigrees with familial transmission, there is marked variability of cardiac morphology, including the site of hypertrophy and functional limitation.

Neurohormonal factors and hypertension. The fact that morphologic evidence of hypertrophy may not be evident until after the pubertal growth spurt suggests that neurohormonal factors, including reproductive hormones, play a poorly understood role in modulating the expression of hypertrophy. The variability of expression also suggests that, in genetically susceptible patients, the development of hypertrophy may be modulated by exposure to other stresses, such as mechanical stress imposed by athletic activity or even mild hypertension. The role of pressure overload as a possible stimulus for the development of severe hypertrophy in genetically susceptible individuals has been neglected, in part because of the focus on the "pure" forms of unexplained hypertrophy without contamination by factors such as hypertension. It is noteworthy that hypertension was present in the early case report by Brock (29). In this regard, there is new recognition of the syndrome of hypertensive hypertrophic myopathy, which is defined as the presence of severe left ventricular hypertrophy in older patients with a variable history of hypertension in which symptoms, cardiac geometry, presence of mitral annular calcification and systolic and diastolic function simulate hypertrophic cardiomyopathy in the elderly (85). Careful pedigree analysis, histologic studies and ultimately advances in molecular biology are needed to clarify whether this syndrome is completely distinct from hypertrophic cardiomyopathy in the elderly (86) or is possibly a phenotypic expression of hypertrophic cardiomyopathy that is triggered by the appearance of systolic hypertension during aging (87).

Genetic defects. An important future direction in hypertrophic cardiomyopathy will be the confirmation or refuting of the hypotheses that the familial form is a single gene defect with protean manifestations or a combination of several separate genetic defects. Available pooled data suggest an increased frequency of HLA DR4, A9, B5 and B40 antigens in populations of patients with hypertrophic cardiomyopathy, which lends support to a genetic component; however, as yet there has been a failure to demonstrate HLA antigen or other gene product linkage within families to support the concept that hypertrophic cardiomyopathy has a single or closely linked gene loci that determine disease susceptibility (88,89). Attempts are ongoing to use contemporary molecular genetic techniques to identify a linkage between specific gene products and the expression of the disease to ultimately identify and characterize specific deranged deoxyribonucleic acid (DNA) segments and their chromosomal location. Advances in this direction will be

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important not only in developing highly accurate and sensitive markers of this uncommon disease, but also in attempting to understand the genetic loci that are critical in the regulation of cardiac hyperplasia and hypertrophy in general.

Biologic defects. Just as the critical gene loci are not known, the biologic defects responsible for the expression of hypertrophic cardiomyopathy are not known. It is intriguing that there are case reports of the development of cardiac malformations that mimic hypertrophic cardiomyopathy morphology and function in patients with hereditary subcellular defects of skeletal and cardiac muscle, such as hereditary mitochondrial myopathy (90) and myotonic muscular dystrophy (91), and in patients with hereditary storage disorders such as Fabry's disease (92). These rare experiments of nature suggest that the phenotypic expression of hypertrophy seen in hypertrophic cardiomyopathy can occur as a response to diverse developmental defects in which a common defect is a paucity of normal stress-bearing myocytes.

Defective response of developing cardiac cells to sympathetic stimulation. Two hypotheses to explain the development of hypertrophic cardiomyopathy are currently under scrutiny. Goodwin (2), Perloff (93) and Ferrans and Rodriguez (94) have developed the hypothesis that familial hypertrophic cardiomyopathy is caused by a defective response of developing cardiac cells to sympathetic stimulation. This causes a failure of regression of the fetal pattern of disproportionate septal thickening and myofiber disarray that results in the fetal "programming" of permanently disturbed numbers and regional distribution of myocytes available to hypertrophy in response to later developmental stimuli. Support for the hypothesis comes from the association of hypertrophy with other congenital disorders of neural crest origin, such as neurofibromatosis, lentiginosis and pheochromocytoma, and from experimental studies in animals and myocyte culture that have shown that administration of nerve growth factor, a glycoprotein that enhances sympathetic nerve growth, and norepinephrine can stimulate the development of hypertrophy. Support is also drawn from the apparent hyperdynamic contractile state in hypertrophic cardiomyopathy and from the clinical improvement seen with beta-adrenergic blockers. The perception that the hypertrophied myocyte is a hyperdynamic "superman" that can be tamed by negative inotropic agents has been seriously challenged by recent studies (95,96) of stress-shortening and end-systolic pressure-volume relations in patients with hypertrophic cardiomyopathy, which indicate that myocardial contractility is normal or depressed and not hyperdynamic. Kawai et al. (97) reported the presence of normal plasma and elevated myocardial catecholamine content in patients with hypertrophic cardiomyopathy, but others (98,99) have failed to substantiate altered levels of myocardial cyclic adenosine monophosphate (AMP), beta-adrenergic receptor density or adenylate cyclase activity in response to adrenergic agonists in these patients. These observations do not exclude the hypothesis that defective interplay between the cardiac cell and catecholamines may occur in utero and may not be detectable during later development.

Defective regulation of cytosolic calcium: abnormal calcium regulation. A second hypothesis is that the unique biologic defect in hypertrophic cardiomyopathy is the defective regulation of cytosolic calcium. This hypothesis is supported by the clinical association of hypercalcemia and hypertrophic cardiomyopathy (100), the apparent hyperdynamic contractile state and the impairment of diastolic relaxation that can be induced by experimental calcium overload (101). The concept of abnormal calcium regulation has provided an attractive rationale for the use of calcium channel blockers in hypertrophic cardiomyopathy. Recently, Morgan and Morgan (102) studied myocardial tissue obtained at surgery from patients with hypertrophic cardiomyopathy and reported that this cardiac muscle showed a marked prolongation of the cytosolic calcium transient in association with a prolongation of the time course of tension decay. However, subsequent studies from this laboratory (103) have shown similar changes in the intracellular calcium transient in association with secondary pressure overload hypertrophy. As recently reviewed elsewhere (64), current data strongly suggest that changes in the regulation of calcium by the sarcoplasmic reticulum and the sarcolemma are not unique to hypertrophic cardiomyopathy but instead are a characteristic adaptation of advanced pressure overload hypertrophy. Thus, impaired regulation of cytosolic calcium is a likely candidate as an important pathogenic mechanism in hypertrophic cardiomyopathy, particularly when the stress of ischemia, which further impairs calcium handling, is superimposed. However, available evidence does not yet support the hypothesis that calcium overload is the primary genetically determined defect in hypertrophic cardiomyopathy.

Restrictive Cardiomyopathy

Definition and etiology. Of all the forms of cardiomyopathy, this type is the one encountered least frequently. In its classic form, restrictive cardiomyopathy manifests as congestive heart failure with a small or only mildly enlarged heart, mimicking constrictive pericarditis. The pathophysiology is that of impaired diastolic function, attributable to decreased ventricular distensibility and impairing diastolic filling secondary to morphologic changes in the endocardium or myocardium or both. In the tropics, the most prevalent form of restrictive cardiomyopathy is endomyocardial fibrosis, which is not really a disease of heart muscle, but primarily a disease of the endocardium, which becomes scarred and thickened, leading to restriction of ventricular filling and diastolic dysfunction (26). However, the subendocardial myocardium is often involved, as are the AV valves, which become insufficient. Characteristically, the

outflow tract is spared. In the Ivory Coast, 20% of deaths due to heart failure before age of 40 are attributed to this disease (26).

Tropical endomyocardial fibrosis was first reported in 1946 by Bedford and Konstam (104). Ten years earlier, Löffler (105) in Switzerland had described a similar disease in the West, associated with eosinophilia, which he named endocarditis parietalis fibroplastica and that has since become known as Löffler's endocardial fibrosis and has been reported from several developed countries. More recently, it has been proposed that these are related or identical diseases, the eosinophilia having preceded the clinical manifestations and being observed only rarely in the tropics (106). The cardiac manifestations have been reported to be associated with degranulation of eosinophils and their severity to be a function of the severity and duration of eosinophilia. Thus, a pathogenetic role has been attributed to degranulated eosinophils, which have been found to bind immunogammaglobulin IgG and have an increased peroxidase, which in turn was demonstrated to have direct toxic effects on rat myocytes (107).

In the West, myocardial restriction is more common than endocardial restriction. The most frequent forms are idiopathic myocardial fibrosis and amyloid heart disease, the latter by definition really falling into the category of "specific heart muscle disease." Other specific heart muscle diseases, such as hemochromatosis, sarcoid heart disease, myocardial infiltration by tumor, Fabry's disease and radiation fibrosis may also present as restrictive cardiomyopathy (108). In these instances, the constitutive properties of the ventricular wall are altered: the diffuse increase in fibrous tissue, infiltration by tumor or deposits of foreign substances, for example amyloid, stiffen ventricular walls and thus prevent normal dilation of ventricular chambers during diastole, eventually reducing stroke volume and cardiac output. However, the syndrome of restrictive cardiomyopathy has also been observed in the absence of histopathologic abnormalities of the endocardium or myocardium (109). Some of these cases are attributable to concentric hypertrophy (110). A neglected potential mechanism has been alteration of collagen and the cytoskeleton, such as described by Caulfield (111).

Diagnosis. The diagnosis of restrictive cardiomyopathy, the rarest form of cardiomyopathy, should be entertained in patients who present with congestive heart failure in the presence of slight or no cardiomegaly, and the principal differential diagnosis is constrictive pericarditis. Chest pain is not unusual. Elevation of jugular venous pressure is usually quite prominent. Murmurs of mitral or tricuspid regurgitation, or both, may be heard. Atrial arrhythmias, the brady-tachycardia syndrome, or complete heart block may be present (112,113). In late cases, the ECG may show low voltage. Noninvasive evaluation and hemodynamic study tend to confirm preservation of normal or near normal systolic function in the presence of elevated but not equal left and right ventricular filling pressures. The square root sign (diastolic dip and end-diastolic plateau) is often present.

All patients with restrictive pathophysiology should undergo endomyocardial biopsy (114) to rule out specific heart muscle disease such as amyloidosis. If the histologic features are normal or near normal, constrictive pericarditis should be reconsidered even if echocardiography did not suggest this possibility. Computed tomographic scanning has also been found of value in the differential diagnosis (115).

Treatment. When one sees the extreme interstitial fibrosis or deposition of amyloid surrounding cardiac myocytes, individually or in clusters, it is difficult to think of therapeutic interventions other than nonspecific supportive measures, such as diuretics and vasodilators in cases of congestive heart failure. Even here, caution must be exercised because elevated ventricular filling pressures may be needed for adequate stroke volume and cardiac output. On the other hand, as long as idiopathic cases exist without such morphologically evident "restriction," the search must continue for other mechanisms that might lead to specific therapy. For example, vascular lesions and spasm resulting in ischemia have been incriminated in the myocardial fibrosis encountered in scleroderma (116). Contraction band necrosis of myofibers (117) and abnormal thallium scans in the presence of normal coronary angiograms (118) point in this direction. Radiation-induced myocardial fibrosis also appears to involve damage to the myocardial microvasculature.

Endocardial fibroelastosis, usually of unknown etiology, has been reported in association with carnitine deficiency (119). Clinically, the detection of low serum carnitine levels, especially in cases of familial cardiomyopathy or endocardial thickening demonstrated by biopsy, may lead to specific therapy with L-carnitine. Another specific heart muscle disease, which may present as specific restrictive cardiomyopathy and be amenable to specific therapy, is hemochromatosis (120); myocardial deposits of iron can be reduced by means of phlebotomies (121) or by chelation (122), resulting in functional improvement. Endomyocardial fibrosis may be treated surgically by endocardiectomy and repair or replacement of affected AV valves (123). Antihypereosinophilic therapy for the hypereosinophilic syndrome with prednisone or hydroxyurea, or both, has been recommended (124). Surprisingly, calcium channel blockers, which are known to improve ventricular diastolic function in hypertrophic cardiomyopathy, have not been studied in restrictive cardiomyopathy.

Dilated Cardiomyopathy

Clinical Features

As indicated before, clinical and pathophysiologic manifestations of dilated cardiomyopathy have been well characterized and are widely known. The characteristic features are impaired systolic function of both ventricles, although

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dysfunction of one ventricle may dominate, leading to manifestations of congestive heart failure. In individuals who have a sedentary lifestyle and low sodium intake, or who are receiving diuretic therapy, even severe systolic dysfunction may not be accompanied by pulmonary or systemic congestion, but rather manifest as easy fatigue and decreased exercise tolerance. Although most clinical cases are recognized when manifestations of heart failure appear, initial presentations as cardiac arrhythmia, conduction disturbance, thromboembolic complication or even sudden death are not uncommon. Such manifestations may even occur before significant ventricular dilation or hemodynamic impairment of myocardial function can be demonstrated.

Although biventricular global hypokinesia, in the absence of risk factors and symptoms of coronary artery disease, would generally permit a clinical diagnosis of dilated cardiomyopathy, especially in young patients, coronary disease may present in just this manner, and dominance of right or left ventricular dysfunction, regional hypokinesia, as well as chest pain may all occur in dilated cardiomyopathy.

Arrhythmogenic right ventricular dysplasia. A cardiomyopathy limited to the right ventricle, associated with arrhythmias and sudden death, especially in young people, has drawn increasing attention (125–127). This rare form of cardiomyopathy is also known as arrhythmogenic right ventricular dysplasia, Uhl's anomaly or parchment heart. Right ventricular myocardium is thinned, partly to completely replaced by fibrous or adipose tissue, and the right ventricle is dilated and hypokinetic. Supraventricular and especially ventricular arrhythmias are characteristically present. Premature death results from early congestive heart failure or sudden, presumably arrhythmic death, which may be the first known manifestation of the disease and not infrequently is associated with physical exertion. Evidence for familial occurrence of this condition has been reported from Italy (128).

Natural course and prognosis. The natural course and prognosis of dilated cardiomyopathy are a function of how early the diagnosis is made. Whereas the annual mortality rate, beginning with the onset of illness, was as low as 5.7% in a series of 258 patients reported on by Kuhn et al. (129), a 1 year mortality rate of 23% and a 2 year mortality rate of 48% have been reported in 87 patients with severe congestive heart failure (130). There is general agreement that significant cardiomegaly, low cardiac output and frank congestive heart failure are associated with a poor prognosis (5,131). In some series, the severity of histopathologic abnormalities on myocardial biopsy correlated inversely with life expectancy (129). Cardiac hypertrophy has a favorable effect on prognosis (132), presumably by limiting systolic wall stress. The presence of etiologic or contributory factors that can be eliminated, for example ethanol, thiamine deficiency, hypertension, anemia and thyrotoxicosis, also may affect the prognosis favorably.

Pathogenesis

Tabulations of "causes" of dilated cardiomyopathy, namely specific agents, diseases and associated syndromes, have been published repeatedly (1–6,8–12). These include, of course, specific heart muscle diseases. Here, we shall focus on proved and postulated pathogenetic mechanisms that may play a role in dilated cardiomyopathy.

Heredity. The familial occurrence of dilated cardiomyopathy is best known in the specific heart muscle diseases associated with hereditary disorders such as glycogen storage diseases, Fabry's disease, mucopolysaccharidosis, the muscular dystrophies and Friedreich's ataxia. Specific biochemical and metabolic abnormalities have been identified in many of these disorders, although cardiac tissue itself has only rarely been studied.

The familial incidence of dilated cardiomyopathy has been given less attention. In a retrospective analysis (133) of 169 patients, the family history was positive in 6.5% of cases. Recently, X-linked, autosomal dominant and autosomal recessive inheritances of dilated cardiomyopathy have been reported (134–136). The use of echocardiography in systematic surveys of relatives of patients with dilated cardiomyopathy promises to reveal a familial prevalence much more frequently than heretofore suspected (137).

A fatal dilated cardiomyopathy in newborn calves has been attributed to a genetic defect (138). The hereditary cardiomyopathy of the Syrian hamster, transmitted by an autosomal recessive gene, has long been a favorite experimental model of dilated cardiomyopathy (139). Major histocompatibility genes have been shown to play a role in the determination of myocardial damage and the immunologic mechanisms involved in infection with cardiotropic viruses (140–142).

It is not unreasonable to expect that within a few years it may become possible to identify individuals genetically predisposed to myocardial disease and to reduce that risk by control of other risk factors, such as ethanol and viral infections.

Nutritional deficiencies. *Thiamine deficiency.* One of the very few curable, as well as preventable, dilated cardiomyopathies is wet beriberi, which is due to deficiency of thiamine or vitamin B_1, a coenzyme essential to the decarboxylation of alpha-keto-acids and in the utilization of pentose in the hexose monophosphate shunt. In the absence of thiamine, oxidative phosphorylation and hence myocardial energy production are impaired. Clinically, thiamine deficiency first manifests as a high output state, secondary to peripheral vasodilation, at least in part attributable to the accumulation of intermediate carbohydrate metabolites. Eventually, the depressed myocardial function in the face of increased preload and wall stress leads to congestive heart failure, first in the presence of normal to high cardiac output, later in association with a low output state. This sequence is

of great interest inasmuch as the peripheral vasodilation undoubtedly acts to delay the onset of left ventricular failure. Indeed, administration of thiamine, resulting in reversal of the peripheral vasodilation, has been reported to precipitate left ventricular failure (143). A similar protective role of naturally occurring left ventricular unloading by peripheral vasodilation is seen in hyperthyroidism and in cirrhosis of the liver.

Selenium deficiency. Another treatable as well as preventable form of dilated cardiomyopathy is that due to selenium deficiency, reported primarily in northeast China, where it is known as Keshan disease (144). The absence of selenium results in decreased activity of glutathione peroxide, an enzyme dependent on selenium, as well as an increase in free radicals that may be toxic to cardiac myocytes. Clinical cardiomyopathy due to a deficiency in selenium has also been reported from the West (145).

Carnitine deficiency. Deficiency of carnitine may present as dilated cardiomyopathy. In this condition, oxidation of fatty acids is impaired and lipids accumulate in the cytoplasm. The deficiency may be familial, and the cardiac lesions are often associated with endocardial fibroelastosis. Oral therapy with L-carnitine is effective (119). Recent reports of therapeutic benefit of carnitine treatment in the cardiomyopathic hamster (146) and in experimental Adriamycin (doxorubicin hydrochloride) toxicity (147) raise the possibility that carnitine deficiency may be a contributory factor in human cardiomyopathies as well. Indeed, Regitz et al. (148) reported reduced myocardial carnitine levels in 30 patients with end-stage heart failure secondary to cardiomyopathy, but also in 22 patients with heart failure secondary to coronary disease.

Toxins and drugs. *Ethanol.* In many populations and series of patients with dilated cardiomyopathy, a history of chronic alcoholism is so prominent that some consider ethanol the major cause of dilated cardiomyopathy (149). Although Mackenzie (150) introduced the term "alcoholic heart disease" in 1902, in the first half of this century congestive heart failure in patients with chronic alcoholism was generally attributed to nutritional deficiencies. In 1957, however, Brigden and Robinson (151) reintroduced "alcoholic heart disease." Indeed, depression of myocardial function by chronic intake of ethanol has been well demonstrated in humans as well as in experimental animals (152–155). However, many efforts to produce chronic congestive heart failure by administration of ethanol alone in animal models have failed. Most recently, however, Edes et al. (156) succeeded in producing dilated cardiomyopathy in young turkeys fed ethanol, accounting for 35% of caloric intake, for 16 weeks. Considerable evidence favors the view that other factors may be needed for full expression of the clinical syndrome of dilated cardiomyopathy, including genetic predisposition, malnutrition, infection and other toxins (23,157). There is increasing evidence for a role of altered handling of calcium, the effects of which may be prevented by verapamil (158). Clinically, the identification of a history of alcoholism in a patient with dilated cardiomyopathy is important inasmuch as the prognosis may be improved by abstention.

Anthracyclines. Doxorubicin (Adriamycin) and daunorubicin, among the most effective agents in the chemotherapy of malignant neoplasms, are highly cardiotoxic. The chronic effects, which include dilated cardiomyopathy, have been studied extensively in humans as well as experimental animals. These studies lead to the conclusion that we may be dealing with a multifactorial pathogenesis, including altered nucleic acid synthesis (159), altered mitochondrial respiration (160), release of vasoactive substances (161), formation of free radicals (162) and calcium overload (163).

Vasoactive agents and microvascular spasm. Studies of cardiac effects of catecholamines have dealt primarily with acute effects, including myocardial necrotic foci resembling ischemic lesions, that have been attributed to microvascular spasm and hypoxia, altered membrane permeability and calcium overload (164). Late effects of acute administration of isoproterenol to rats, however, include cardiomyopathy and congestive heart failure (165). Catecholamine-induced dilated cardiomyopathy in humans is seen most clearly in patients with pheochromocytoma. This form of cardiomyopathy is reversible by removal of the tumor or by adrenergic blockade (166,167).

Of wider interest is the evidence that catecholamines play a role in anthracycline cardiotoxicity (161) and diabetic cardiomyopathy (168). Catecholamines also enhance the severity of necrosis seen in the hereditary cardiomyopathy of the Syrian hamster (169).

Recent studies of experimental models of cardiomyopathy have revealed evidence of microvascular spasms in the cardiomyopathic hamster (170), the hypertensive-diabetic rat (171) and the mouse infected with Trypanosoma cruzi (172). Furthermore, these lesions could be prevented by verapamil, suggesting that calcium overload plays a role in these experimental models, which closely resemble the human disease.

Decreased coronary flow reserve. The frequent occurrence of chest pain, often indistinguishable from angina pectoris, in patients with dilated cardiomyopathy has long puzzled clinicians and has led to the postulate of a decrease in maximal coronary blood flow (173). Cannon et al. (174) studied the responses of coronary blood flow in 26 patients with dilated cardiomyopathy and angiographically normal coronary arteries to ergonovine, dipyridamole and rapid atrial pacing. In the subset of patients with a history of angina pectoris, there was a greater response to ergonovine and a significantly decreased coronary flow reserve in response to either dipyridamole or pacing. Recently, DeMarco et al. (175) reported evidence that in patients with chronic heart failure due to either chronic coronary artery disease or dilated cardiomyopathy, both rest coronary blood flow and

myocardial oxygen consumption were increased and coronary sinus oxygen content was decreased. Although the mechanism of this decreased coronary flow reserve remains uncertain, myocardial hypoxia not only may explain the anginal pain, but also may be implicated as a factor potentially contributing to ongoing myocyte necrosis, replacement fibrosis and deterioration of myocardial function.

Tachyarrhythmia. Reversible heart failure associated with rapid supraventricular arrhythmias has been recognized in patients without evidence of heart disease for some time (176). In a recent report, Packer et al. (177) described eight subjects with uncontrolled tachycardia of long standing associated with depressed left ventricular function, which was at least partly reversed by control of the tachycardia. They thus coined the term "tachycardia-induced cardiomyopathy." It is, of course, possible that they were dealing with subclinical cardiomyopathy enhanced by tachycardia. On the other hand, heart failure has been induced by chronic, rapid cardiac pacing in healthy dogs, followed by persistence of abnormal cardiac function on return to sinus rhythm (178). Underlying mechanisms may include shortening of diastole, depletion of high-energy substrate (179) and ischemia secondary to decreased coronary flow reserve (see earlier discussion). Evidence that supraventricular tachycardia depresses both systolic and diastolic myocardial reserve in patients with established dilated cardiomyopathy was recently reported by Feldman et al. (180), and studies (181) of isolated cardiac muscle from patients with end-stage heart failure yielded evidence for calcium overload and decreased concentrations of cyclic adenosine monophosphate at high frequencies of stimulation.

Calcium overload. The important role of calcium in excitation/contraction coupling and, hence, in the pump function of the heart has long been recognized (182–184). Increasing evidence, derived from studies of both clinical and experimental cardiomyopathies, points toward abnormalities in the handling of calcium by heart muscle cells. Thus, there is evidence of impaired calcium regulation in several experimental models of cardiomyopathy. Myocardial calcium is increased in the cardiomyopathic hamster (185,186). Left ventricular function is improved by the calcium blocker verapamil (187). Calcium overload has also been demonstrated in experimental Adriamycin toxicity (163). In healthy Syrian hamsters fed ethanol until adenosine and high energy phosphates along with left ventricular function became depressed, administration of verapamil along with ethanol was shown to have a preventive effect (158). On the other hand, streptozotocin-induced diabetes in the rat was associated with depression of the calcium pump, reversible by insulin (188). Recent studies (189) of human heart muscle from patients with end-stage heart failure, including cases of dilated cardiomyopathy, also yielded evidence of abnormal intracellular calcium handling.

Oxygen free radicals. Oxygen free radicals have been recognized as toxins that may play a role in several disease processes, of which ischemia/reperfusion injury has been given special attention (190,191). The formation of free radicals has been reported in the cardiomyopathy of the Syrian hamster (192), as well as in Adriamycin toxicity (162). In acute but not in chronic experimental Adriamycin cardiomyopathy, the free radical scavenger alpha-tocopherol (vitamin E) has been found to be of protective value (193).

Infection. All infectious organisms that are capable of invading the blood stream may enter the myocardial capillaries and reach the myocardium. Acute necrotic or inflammatory lesions have been associated with many bacterial, spirochetal, rickettsial, viral, mycotic, protozal and helminthic infections (5,9). Some forms of acute myocarditis have long been recognized as precursors of chronic dilated cardiomyopathy. Thus, both clinical and experimental studies have established that the chronic dilated cardiomyopathy so prevalent in Central and South America and known as Chagas' disease is a late sequel of acute myocarditis due to Trypanosoma cruzi (194–196). Dilated cardiomyopathy has also been recognized as a late sequel of African trypanosomiasis (197) and of toxoplasmosis (198).

Viral myocarditis. Increasing evidence also points to dilated cardiomyopathy as a late sequel to acute viral myocarditis (199). This evidence includes clinical follow-up studies (200–206). Support of such a relation has also come from serologic surveys of patients with chronic dilated cardiomyopathy (207–209).

Not all viruses, however, are myotropic and not all patients infected with myotropic viruses develop myocarditis or dilated cardiomyopathy, or both. This observation should not surprise, in view of the great differences in susceptibility to and expression of cardiac involvement by a given virus seen in different inbred strains of rodents (140,141). Although it has been postulated that the majority of cases of idiopathic dilated cardiomyopathy in countries in which Trypanosoma cruzi is not endemic may be of viral origin (48,210), the fraction of cases for which this holds true is unknown.

HIV virus (AIDS). Acute as well as chronic dilated cardiomyopathy is encountered with increasing frequency in patients with acquired immunodeficiency syndrome (AIDS) (211), often associated with evidence of myocarditis (212). The majority of cases remained unrecognized before postmortem examination and may have been associated with opportunistic infections. However, HIV virus has been cultured for myocardial tissue at least once (213), although it may have originated from perfusing blood. As yet, cardiac involvement has not been reported to occur in experimental models of infection with this or related viruses. Therefore, it remains an open question whether the HIV virus itself is responsible for cardiomyopathy.

Experimental myocarditis. Strong support for dilated cardiomyopathy as a sequel to acute myocarditis also is provided by extensive studies of experimental models of myocarditis. Thus, the chronic form of Chagas' disease has been reproduced in mice (196), and chronic cardiomyopathy has been demonstrated to develop in mice infected with encephalomyocarditis virus (214,215), herpes simplex virus (216) and especially with coxsackievirus B3 (217) and B4 (218).

Subacute and chronic myocarditis. Myocarditis may also be subacute and even chronic. In humans, this condition was first described in 1931 by Boikan (219), who coined the label "myocarditis perniciosa." Additional cases were reported by Kline and Saphir (220). With increasing use of endomyocardial biopsy (221) in patients with chronic dilated cardiomyopathy, the persistence of active inflammation and necrosis has been reported in 3% to 63% of such cases, especially if heart failure was <1 year's duration (222–226). This variability may, in part, be attributed to variable criteria for the histopathologic diagnosis of myocarditis (227). However, since the establishment of strict criteria for the histopathologic diagnosis of active myocarditis (228), the prevalence of active myocarditis among patients with dilated cardiomyopathy has been reported to be closer to 10% (229). Chronic myocarditis associated with demonstrably persistent Trypanosoma cruzi infection has also been described (230).

Recent application of in situ hybridization techniques to the study of the pathogenesis of ongoing myocarditis revealed that encephalomyocarditis viral nucleic acid in cardiac myocytes was no longer present 2 weeks after isolation of virus (231). Similar results were obtained in experimental coxsackievirus B3 infection (232) and in myocardial biopsies from patients with cardiomyopathy and myocarditis (233,234). Thus, the question of a pathogenetic role of persistent viral infection in subacute and chronic myocarditis must be reconsidered.

Immune/autoimmune mechanisms. Experimental myocarditis has been produced by immunization with myocardial proteins (235–238). The fact that trypanosomes can be demonstrated only rarely in subacute and chronic Chagas' cardiomyopathy has led to the concept of chronic Chagas' disease as an autoimmune disease, borne out by extensive clinical and experimental studies (239). Recent experimental studies (240) suggest that this form of auto-immune myocarditis is attributable to cross-reacting antigens of Trypanosoma cruzi and skeletal muscle, presumably mediated by cytotoxic T lymphocytes. Furthermore, an experimental myocarditis induced in mice by homologous heart immunization has been shown to resemble chronic murine Chagas' cardiomyopathy (241).

Inasmuch as the isolation of cardiomyotropic viruses from myocardium only rarely is possible later than 2 weeks under inoculation or infection, subacute and chronic myocarditis, as well as later noninflammatory cardiomyopathy, have also long been considered of immune or autoimmune origin. A great deal of evidence has accumulated in favor of immunopathogenesis of myocarditis and its late sequel of cardiomyopathy, derived from studies of humans and experimental animals, and several monographs and reviews have been published recently (242–248).

Humoral and cellular immunity mechanisms. Both in humans and in experimental animals, there is evidence that either humoral or cellular immunity, or both, may play a role in expression of both acute and chronic effects of viral replication in the heart. Evidence to date indicates that many different mechanisms may be operative, that these involve cytotoxic T lymphocytes, suppressor T lymphocytes and natural killer (NK) cells, and that the mechanisms as well as the biologic effects may be a function of genetic background, type and strain of virus, age, gender, species and strain of the host as well as other modifying factors such as stress. That immune processes are involved even in the expression of acute myocarditis was first demonstrated by Woodruff and Woodruff (249), who found that depletion of T lymphocytes in mice infected with coxsackievirus B3 significantly suppressed both cellular infiltration and necrosis in the myocardium. Since then, evidence has accumulated for a cytotoxic role of T helper cells (L3T4) and T cytolytic/suppressor cells (Lyt 2+), and for a myocardial protective role by activated natural killer (NK) cells and suppressor T lymphocytes (247,250). Evidence has also been presented for deficient natural killer cell activity in patients with dilated cardiomyopathy (251,252).

Degeneration of cardiac ganglia. The well known dysautonomia associated with degeneration and loss of cardiac ganglia in Chagas' disease led Amorim and Olsen (253) to study seven hearts from patients with dilated cardiomyopathy. They found a significant loss of ganglion cells in the sino-atrial region, whereas collagen tissue was increased. Neither the cause of this neuronal degeneration nor its functional significance is known, nor is it clear whether this is a primary or a secondary phenomenon or even an epiphenomenon.

Alterations in the cardiac cytoskeleton. Noncontractile elements of the myocardium have been relatively neglected in the search for pathogenetic mechanisms in dilated cardiomyopathy. Yet, myocytes are surrounded by a network of bundles of collagen that are below the limits of resolution of light microscopy and best studied by means of scanning electron microscopy (254). Alterations of the collagen matrix have been observed in experimental cardiac hypertrophy (255) and also after a single injection of Adriamycin in rats (256).

"*Interstitial heart disease.*" A correlative study of histopathology and left ventricular function in 24 patients with dilated cardiomyopathy by Nakayama et al. (257) reported a relation of degree of impairment of ventricular function with proliferation of collagen fibers. More recently, studies of the

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collagen matrix in three postmortem hearts from patients with dilated cardiomyopathy by Weber et al. (258) revealed evidence for pathologic remodeling of collagen, involving a shift from a stronger to a weaker type of collagen. The authors hypothesized that these changes may play a role in cardiac dilation and hence put forward the concept of "interstitial heart disease" and recommend the substitution of "cardiopathy" for "cardiomyopathy."

Diagnosis

In view of the protean manifestations and initial presentations of dilated cardiomyopathy already mentioned, an awareness of its existence and prevalence is paramount for its detection. The failure to diagnose dilated cardiomyopathy is most frequently seen in the early stages of the disease in association with the custom of limiting cardiac diagnosis to labeling of manifestations, such as "cardiac arrhythmia" or "congestive heart failure," and in the mislabeling of dilated cardiomyopathy as ischemic heart disease attributable in part to the latter's high prevalence. Occasionally, insufficiency of either or both AV valves may lead to a misdiagnosis of valvular heart disease. In most cases, however, careful clinical evaluation and judicious use of noninvasive methods, such as echocardiography and radioventriculography, should lead to the correct diagnosis.

Differentiation from coronary artery disease. There remains, however, a group of patients, especially men, with coronary risk factors, whose myocardial dysfunction is regional and who may give a history of typical or atypical anginal chest pain. Here, coronary angiography is essential. It must also be kept in mind that three vessel coronary disease may be painless and associated with global hypokinesia of the left ventricle. Finally, there are patients with significant coronary atherosclerosis whose myocardial dysfunction appears to be disproportionate to the degree of coronary disease. By definition, as long as significant coronary obstruction exists, these patients cannot be classified as having a cardiomyopathy. Yet, pathogenetically and pathophysiologically, a cardiomyopathic process may exist, and its recognition and identification of causal factors may be of value for purposes of prognosis, therapy and secondary prevention. Of special importance in this regard is the identification of chronic alcohol abuse.

Therapy

Inasmuch as true dilated cardiomyopathies are of unknown origin, treatment is symptomatic and nonspecific as contrasted with specific heart muscle diseases, for many of which specific therapy is available (5). Hence, it is necessary to evaluate every patient with dilated cardiomyopathy for the possible existence of a specific etiology that might identify a specific therapeutic approach. The therapeutic approach to decompensated dilated cardiomyopathy differs little from that to congestive heart failure in general and was reviewed in depth in a recent contribution by Parmley (259) to this Anniversary series of articles and also by Cohn (260). The discussion here will be limited to considerations of special relevance to dilated cardiomyopathy.

Diuretics. In the use of diuretics, it should be kept in mind that loss of electrolytes and water-soluble vitamins may affect the structure and function of myocardium adversely, and that excessive volume depletion may result in depression of ventricular filling pressures below the optimal level.

Vasodilators. Vasodilators represent the major advance in the therapy of dilated cardiomyopathy in recent years. Unlike ischemic heart disease, an arterial pressure significantly below normal may be acceptable in dilated cardiomyopathy; thus, higher doses of vasodilators may be tolerated. However, the physician must be alert to possible deleterious effects on cerebral and renal function (261). Evidence for prolongation of life has been demonstrated for the combination of hydralazine and isosorbide dinitrate (262) and for converting enzyme inhibitors (263).

Digitalis and inotropic agents. Digitalis glycosides, albeit now recognized as relatively weak positive inotropic agents, are still of value in these patients (264,265). In cases of intractable, advanced congestive heart failure, hospitalization and a course of intravenous amrinone or dobutamine, under close supervision, may initiate diuresis and result in considerable symptomatic and objective improvement (266,267). Such a course may have to be repeated every few weeks. A sophisticated recent study of the physiologic mechanisms determining the hemodynamic response to dobutamine demonstrated significant differences in responses between a group with appropriate and another with inappropriate hypertrophy, the latter exhibiting a significantly attenuated response (268).

Calcium channel blockers. The considerable evidence for a role of calcium overload and the preventive value of verapamil (see earlier) in several experimental forms of cardiomyopathy, as well as circumstantial evidence for a role of myocardial hypoxia, have led to a number of efforts to treat dilated cardiomyopathy with calcium antagonists, recently reviewed by Colucci (269). Evidence for negative inotropic effects of these agents has limited their clinical use in advanced dilated cardiomyopathy; controlled trials, especially in the early stages, should be considered.

Antiarrhythmic agents. High grade ventricular ectopic activity is frequent in dilated cardiomyopathy, generally correlating with the severity of systolic dysfunction and often responding to therapeutic improvement of ventricular function. Pharmacologic approaches to the management of arrhythmias in this setting have been discussed recently by Myerburg et al. (270).

Beta-adrenergic blockers. Waagstein et al. (271) first reported beneficial effects of treatment of patients with dilated

cardiomyopathy and a high rest heart rate with beta-adrenergic blockade. This approach has its conceptual justification inasmuch as it addresses the increased activity of the adrenergic nervous system in congestive heart failure, initially blocks the beta-adrenergic receptors and then permits up-regulation of the $beta_1$-receptors down regulated by the chronic effects of norepinephrine (272). However, the negative inotropic effects of beta-blockade justifiably have been of concern. A number of uncontrolled studies (273,274), however, have suggested the value of this approach. Until the results of controlled trials now in progress become available, clinical use of this mode of therapy best be restricted to patients with tachycardia and patients in relatively early stages of the disease.

Coenzyme Q_{10}. Several studies have been reported of therapy of patients with dilated cardiomyopathy with coenzyme Q_{10}, a redox coenzyme of several mitochondrial enzymes (275,276) that has been believed to be deficient in diseased hearts. Further study appears warranted.

Anticoagulants. In view of the high incidence of thromboembolic complications, all patients with dilated cardiomyopathy and chronic heart failure, unless there is a contraindication, should receive therapy with a coumarin derivative. This therapy has been validated (277).

Cardiac transplantation. Inasmuch as many patients with dilated cardiomyopathy are young and free of systemic disease yet carry a guarded prognosis, cardiac transplantation, with its rapidly improving prognosis, has much to offer and should be considered before secondary changes in the pulmonary and systemic circulation have become irreversible. Indeed, approximately half of all patients undergoing transplantation to date have suffered from dilated cardiomyopathy. The timing of cardiac transplantation remains a challenge (278–280).

Prevention

At this time, the limited knowledge about the etiology of dilated cardiomyopathy does not permit primary prevention. However, a few words about secondary prevention are in order. The principle is simple: inasmuch as myocardial damage may be pluricausal and cardiac toxins may be additive, a patient with cardiomyopathy must be protected from potential cardiotoxins, such as ethanol, anthracyclines, radiation, nutritional deficiency, electrolyte imbalance, as well as excessive preload and afterload such as imposed by anemia and hypertension.

Summary and Conclusions

The cardinal clinical and pathophysiologic characteristics, as well as current concepts of pathogenesis and therapy of the principal forms of cardiomyopathy, have been reviewed with emphasis on recent developments and unsolved questions.

In the last 40 years, understanding of the diseases of heart muscle has advanced from clinical descriptions, first to pathophysiological understanding and, more recently, to gradual unveiling of likely pathogenetic mechanisms. The application of techniques of molecular biology and genetics is just beginning to bear fruit. Much of the progress has been facilitated by the development of experimental models of heart muscle disease, and we owe much to the contributions made by experimental animals. The use of isolated and cultured heart muscle cells is still in its infancy, and better techniques for culturing adult myocytes are needed. A major difficulty encountered in research of human cardiomyopathies, and to a lesser extent of experimental cardiomyopathies, is the differentiation between primary, causal and secondary abnormalities in structure and function. Thus, greater emphasis must be placed on studying early, pre-heart failure stages of cardiomyopathy.

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