SYMPOSIUM
Cardiomyopathy

Introduction

By CHARLES K. FRIEDBERG, M.D.

THIS SYMPOSIUM calls attention to a disease or a cluster of similar diseases that have engaged increasing interest and have been recognized with increasing frequency but continue to defy our efforts at resolving its cause, defining positive criteria for clinical diagnosis, and undertaking effective measures for prevention or specific treatment. Lack of greater progress in these matters has not been due to inadequate discussion of the subject in the form of conferences, seminars, lectures, review articles, and symposia. In 1964, three issues of Progress in Cardiovascular Diseases were devoted to "Primary myocardial diseases and the cardiomyopathies," and in November, 1965, Circulation published a symposium entitled "Clinical recognition and treatment of primary myocardial disease." The present symposium is designed to update the latter and is based in part on a symposium on cardiomyopathies presented at the November 1970 meeting of the American Heart Association. However the contributors were asked to modify their material substantially in order to present a teaching review instead of a report confined essentially to their own findings. Dr. Perloff, who moderated the 1970 symposium and who played a major part in editing the papers of this symposium, was asked to write an overview of the general subject of the cardiomyopathies in place of his presentation, entitled "Cardiomyopathies of heredofamilial neuromyopathies," which has since been published in the May 1971 issue of Modern Concepts of Cardiovascular Disease. Drs. Demakis and Rahimtoola, who did not participate in the 1970 symposium, contributed a manuscript on peripartum cardiomyopathy. This symposium is limited to a few aspects of cardiomyopathy which are of current interest and importance, but Dr. Perloff's overview provides a broad perspective which encompasses the entire subject insofar as limited space permits.

Terminology, when properly chosen and defined, should promote clarity of understanding and accuracy of communication. In the field under consideration the choice of multiple terms and their varied definitions have served rather to handicap understanding and communication. At present there is increasing agreement to use the term cardiomyopathy, and appropriate definitions and classifications are discussed by Dr. Perloff. It would seem desirable to abandon the term primary myocardial disease, especially as a synonym for cardiomyopathy, since primary myocardial disease has been employed very broadly to include forms of myocardial disease that on clinical and other grounds should not be grouped with cardiomyopathies, e.g. acute specific and nonspecific myocarditis, myocardial disease due to hyperthyroidism or hypothyroidism or anemia, and primary neoplasms of the heart.

Etiology

Three of the contributions to this symposium have important etiologic connotations,
and Dr. Perloff has commented on the various etiologic types of cardiomyopathies in one of his major classifications of this group of diseases. Like other diseases of unknown etiology, idiopathic cardiomyopathy has been attributed to a variety of causes including viral infections, immune reactions, toxic factors, genetic factors, and metabolic and nutritional disturbances. The role of metabolic disturbance appears clearly established in the nonidiopathic cardiomyopathies in which myocardial structure and function are grossly disturbed by infiltration of foreign material as in cardiac amyloidosis, hemochromatosis, glycogen storage, and the mucopolysaccharidoses. However, there is no direct evidence that the idiopathic forms of cardiomyopathy, which are characterized by myocardial hypertrophy and generally sparse fibrosis, are due to metabolic disturbances. Nutritional disturbances are strongly suggested in the cardiomyopathies of oriental beriberi and in the African cardiomyopathies, which are associated with severe malnutrition especially with respect to protein intake, but the role of nutritional disturbance in idiopathic cardiomyopathy has not been satisfactorily demonstrated. In the absence of an established cause, genetic abnormalities with possible enzymatic disturbances may be postulated, and this is supported for at least some cases by the frequent familial occurrence of idiopathic hypertrophic obstructive cardiomyopathies and in the heredofamilial neurologic diseases associated with cardiomyopathy.

In this symposium particular consideration is given to the role of viral infections, alcohol, and late pregnancy and the postpartum period in cardiomyopathy. With respect to viruses, it is essential to distinguish between their possible detrimental effect on cardiac function in patients with underlying cardiac disease, the relation of viral infection of the fetus to congenital cardiac anomalies, their possible role in causing an acute or prolonged myocarditis by direct infection or an immune mechanism, and any postulated causal relationship to idiopathic cardiomyopathy. The reports of the production of myocarditis in the experimental animal should be interpreted with caution insofar as they are applied to human myocarditis, and the findings appear to have even less applicability to idiopathic cardiomyopathy. It has long been tempting to postulate that idiopathic cardiomyopathy is the result of a previous acute myocarditis and that the inflammatory changes in the myocardium have undergone fibrosis by the time the heart is examined at autopsy. Indeed, there is an occasional patient who presents with the clinical picture of pericarditis or of pericarditis and myocarditis with the apparent later development of a chronic cardiomyopathy, but as a rule no relationship can be established between idiopathic cardiomyopathy and a preceding viral infection or myocarditis. The reports on the presence of bound globulin in the myocardium and of circulating antmyocardial globulins in patients with idiopathic cardiomyopathy, which might suggest that the latter is an autoimmune disease, have been inconsistent.

The possible relationship to alcohol is quite another matter. The deleterious effect of acute as well as prolonged ingestion of alcohol on cardiac function and the ultrastructural changes in the myocardium attributed to alcohol are discussed by Dr. Regan. Evidence is also provided that these cardiac lesions and functional disturbances attributed to alcohol are independent of nutritional deficiency. There is strong clinical support for an etiologic relationship of alcohol to idiopathic cardiomyopathy in the relatively high incidence of significant background of alcoholism, when a searching history is taken from the patient's family and friends as well as from the patient himself. Furthermore it is in those patients with cardiomyopathy who have such a background of alcoholism that reversal of both heart failure and cardiomegaly are most likely to occur with abstention from alcohol. Recurrence is also seen when alcohol is resumed. However, these observations do not apply to the majority of patients with idiopathic cardiomyopathy who have neither a history of

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excessive intake of alcohol nor a satisfactory clinical response to complete abstention.

The use of the title “Peripartum cardiomyopathy” in the presentation of Demakis and Rahimtoola points up a dilemma which is, at the same time, a stimulating challenge to seek possible etiologic clues. Approximately 90% of the patients in this category appear to contract their cardiomyopathy in the first 5 months after delivery but in the remaining patients the apparently identical disease develops in the last month of pregnancy. In those in whom the disease first appears more than 1–2 weeks after delivery (postpartum cardiomyopathy) neither the stress of pregnancy nor of labor can be invoked as a cause. Even those who suffer the disease in the last month of pregnancy have passed the peak of the hemodynamic strain of pregnancy. These observations appear to suggest that pregnancy and labor are unrelated to the cardiomyopathy, and the postpartum period is a coincidental state. Or does the disease become manifest when and because pregnancy by some hormonal or other factor no longer provides protection?

Asymptomatic Idiopathic Cardiac Hypertrophy

At one time cases of idiopathic cardiomyopathy were described under the heading of “idiopathic hypertrophy of the heart.” The latter term appears particularly applicable as a description when the disease is characterized clinically by cardiac enlargement on X-ray examination and by left ventricular hypertrophy in the electrocardiogram in the absence of symptoms. There may be no cardiac murmurs to suggest complicating or associated valvular insufficiency. In the absence of the hemodynamic stresses which are usually associated with and underly the development of cardiac dilatation and hypertrophy, and in the absence of heart failure which may cause hypertrophy by the stimulus of stretch or dilatation, the mechanism of cardiac hypertrophy in idiopathic cardiomyopathy is even more obscure than in other forms of heart disease.

Clinical Considerations

Certain clinical considerations deserve comment. Although the diagnosis of idiopathic cardiomyopathy is being made in the physician’s office or at the bedside with increasing frequency, many cases are undiagnosed, or the diagnosis is listed with uncertainty as one of a number of possibilities. For practical diagnostic purposes idiopathic cardiomyopathy should be considered in the categories of (1) unexplained cardiac enlargement or hypertrophy with or without other clinical manifestations, (2) unexplained congestive heart failure especially if heart failure follows unexplained cardiac enlargement without heart failure, and (3) outflow tract obstruction with features atypical for valvular aortic stenosis. Restrictive cardiomyopathy should not be regarded as a clinical entity since such a concept may lead to confusion. There is particular danger that this diagnosis, made improperly in a patient with constrictive pericarditis, should lead to the omission of the required surgical treatment.

Diagnosis

Although bookside clinicians can find exceptions to the following suggestions, they are useful and generally accurate approaches to the diagnosis of idiopathic cardiomyopathy. Of necessity, the diagnosis depends in large measure on exclusion of other common varieties of cardiac disease, but positive characteristic features should also be emphasized. Unless cardiomyopathy provides protection against coronary disease or hypertension, or unless these cardiac diseases and rheumatic cardiovalvular disease prohibit the development of idiopathic cardiomyopathy, one may expect that cardiomyopathy will occasionally coexist with other forms of heart disease in the same patient. This association will not be recognized so long as the diagnosis of cardiomyopathy requires the exclusion of all other possible cardiac diseases. The absence of other etiologic forms of heart disease does indeed afford diagnostic support, but positive criteria must be developed for the diagnosis of cardiomyopathy even in the presence of other heart disease.
Cardiac Hypertrophy due to Cardiomyopathies. Idiopathic cardiomyopathy should be suspected whenever cardiac enlargement and/or cardiac hypertrophy is discovered or verified by X-ray and electrocardiographic examination if there is a previous record of a normal heart size and there was no intercurrent disease, or if there is no history or present evidence of other disease which could account for cardiac enlargement or left ventricular hypertrophy. If, in such apparently idiopathic cases of cardiac enlargement, a differentiation must be made from unexplained pericardial effusion, examination and study by cinefluoroscopy of the epicardial fat lines provides a simple noninvasive technic for such differentiation. Positive findings which would then support the diagnosis of idiopathic cardiomyopathy include: a family history of unexplained cardiac enlargement, syncope, or sudden death below the age of 50 years; a history of prolonged alcoholism; electrocardiographic evidence of left atrial hypertrophy or intraaerial conduction defect with large, notched bizarre P waves; left ventricular hypertrophy pattern on the electrocardiogram with initial slurring of the upstroke of the R wave and/or absent or embryonic Q in lead I and left precordial leads; left atrial enlargement on X-ray examination; the association of frequent or multifocal ventricular premature beats, atrial fibrillation, or paroxysmal ventricular tachycardia without apparent cause; and atrioventricular or intraventricular conduction disturbances in persons less than 50 years of age. (These positive findings, are also applicable to diagnosis in the next two situations, but will not be repeated.) Even when there is some other disease which may be associated with the above findings, cardiomyopathy may be suggested if the findings are irrelevant or disproportionate in degree for the stage or severity of the other disease.

Congestive Heart Failure due to Cardiomyopathy. The second common clinical picture which requires consideration of cardiomyopathy is congestive heart failure in the absence of signs of ventricular outflow obstruction. Other cardiac diseases which could account for the heart failure must be excluded. However when these diseases are relatively mild (e.g. mild or moderate hypertension without severe renal disease, or mild and relatively recent angina pectoris without a history or electrocardiographic findings of myocardial infarction), and the heart failure is a prominent feature, cardiomyopathy is the more likely diagnosis especially if there are positive signs suggesting cardiomyopathy, as indicated above. In some of these patients with heart failure and at most an equivocal history of angina pectoris or myocardial infarction and nonspecific electrocardiographic changes, the various and refractory cardiac arrhythmias, including episodes of ventricular tachycardia and ventricular fibrillation, are highly suggestive of cardiomyopathy. The development of cardiac enlargement and heart failure in the last month of pregnancy or first 5 months postpartum in the absence of a previous history of heart disease or of pulmonary emboli or toxemia during pregnancy indicates cardiomyopathy. Although gallop rhythm, including ventricular gallop, may be present with heart failure of various etiologies, its absence during heart failure would tend to exclude a cardiomyopathy.

Occasionally congestive heart failure due to cardiomyopathy may require differentiation from constrictive pericarditis or pericardial effusion with cardiac tamponade. The constrictive pericarditis is generally excluded by the presence of substantial cardiac enlargement and/or left ventricular hypertrophy. When there is a pericardial effusion in combination with constrictive pericarditis or with cardiac tamponade, and this simulates cardiac enlargement, the differentiation can be suggested by the obliteration of the individual cardiac and vascular contours, the partial concealment of the main hilar vessels, and the clear lung fields in cases of pericardial effusion, with more definitive differentiation by a study of the epicardial fat lines by means of cinefluoroscopy.

The presence of a holosystolic murmur, indicating mitral or tricuspid regurgitation,
poses one of the most difficult problems in distinguishing rheumatic cardiovalvular disease or other causes of mitral regurgitation from that associated with cardiomyopathy. Calcification of a valve and diastolic murmurs tend to exclude cardiomyopathy, but associated ventricular and atrial gallops should not be misinterpreted as a diastolic murmur. Effective treatment for congestive heart failure usually reduces the intensity or abolishes the murmur of mitral regurgitation in cardiomyopathy, but increases the loudness of the murmur in rheumatic valvular disease. The positive indices of cardiomyopathy listed above also aid in differentiating cardiomyopathy with heart failure and a systolic murmur from rheumatic cardiovascular disease.

**Outflow Obstruction due to Cardiomyopathy.** The third major presentation of idiopathic cardiomyopathy, i.e., besides (1) unexplained cardiac enlargement and/or left ventricular hypertrophy and (2) unexplained heart failure or heart failure with certain distinctive associated features, is (3) left ventricular outflow obstruction, suggesting a diagnosis of aortic stenosis. That the patient has idiopathic subaortic stenosis (i.e. obstructive cardiomyopathy) rather than valvular stenosis is indicated by a visible and palpable very rapid rise of the carotid pulse and a Corrigan-like pulse but without the diastolic murmur or low diastolic pressure of aortic regurgitation. There is no aortic or mitral valvular calcification. The aortic ejection systolic murmur is of maximal intensity at the lower left sternal border, usually does not radiate to the neck, is unaccompanied by a thrill or ejection click, and there is disagreement as to whether the murmur is due to mitral regurgitation or aortic stenosis. An associated mitral regurgitation is present in the majority of cases, and this combination of murmurs should lead to a search for other evidence of obstructive cardiomyopathy. A prominent apical impulse is present and this may be double or triple and associated with atrial and ventricular gallop sounds. The electrocardiogram shows not only the pattern of left ventricular hypertrophy but may also disclose prominent notched and widened P waves, Q waves simulating anteroseptal myocardial infarction, and occasionally the preexcitation syndrome. If there is a history of syncope, it occurs promptly after conclusion of an exertion rather than during an exertion as in valvular aortic stenosis.

When a diagnosis of cardiomyopathy has been made, the term idiopathic can be applied only when other known causes of cardiomyopathy have been excluded by appropriate studies. Such causative diseases include particularly amyloidosis, certain neuromuscular diseases, sarcoidosis, hemochromatosis, the mucopolysaccharidoses, systemic sclerosis, and in endemic areas Chagas' disease. When clinical studies including noninvasive technics leave the diagnosis of cardiomyopathy equivocal, cardiac catheterization including cineangiocardiography and coronary arteriography must be undertaken, especially if cardiac or coronary surgery is being contemplated. Occasionally exploration by thoracotomy is justifiable if there is a reasonable probability that constrictive pericarditis rather than a cardiomyopathy is responsible for the clinical picture.

**Treatment**

The treatment of the cardiomyopathies has been discussed in a systematic manner by Dr. Perloff, and with respect to their individual topics by the other contributors. Questions commonly arise in practice with regard to the timing and vigor of certain forms of therapy and the degree of restriction imposed. The use of digitalis, the degree of sodium restriction, and the frequency and dosage of diuretics are determined as in heart failure of other etiology and are modified to obtain maximal clinical response with minimal side effects. Digitalis sometimes offers a problem in the obstructive form of cardiomyopathy because its inotropic effect tends to increase the dynamic obstructions. However, digitalis should be administered if congestive heart failure is a dominant feature, especially if it is associated with atrial fibrillation.

Sometimes when recurrent or intractable heart failure in obstructive or nonobstructive
cardiomyopathy is associated with severe and uncontrolled arrhythmias, treatment of the latter should be emphasized not only for the sake of controlling the arrhythmias but also the heart failure. Digitalis must be given with caution because digitoxic arrhythmias occur commonly either because of increased myocardial sensitivity or overdosage in a vain effort to control the arrhythmia. The insertion of a pacemaker should be considered both to prevent syncopal attacks and to provide protection when various antiarrhythmic agents must be given in large doses and in combination.

Pulmonary and systemic emboli are common occurrences in idiopathic cardiomyopathies, but in this country their presence together with mural thrombus is noted more often at autopsy than as dominant clinical features. The indications and effectiveness of anticoagulants are uncertain. Their use appears justified when there is definite evidence of such emboli and possibly also in the presence of uncontrolled heart failure or a distressing or frequently recurring paroxysmal atrial fibrillation, but the justification for long-term anticoagulant therapy in the absence of such possible indications is dubious.

The question of prolonged bed rest (many months and usually a year or longer), always arises whenever a diagnosis of idiopathic cardiomyopathy is made. The favorable reports of such treatment by Burch and his associates have aroused great interest, and understandably so, when we consider the generally unfavorable outlook and unsatisfactory treatment of idiopathic cardiomyopathy. However the recommended regimen of prolonged bed rest is simply impractical and cannot be justified unless its efficacy is unequivocally established. The studies are uncontrolled and the results have not been shown to surpass results obtained by appropriate and generally similar treatment but without the prolonged bed rest; i.e., the importance of the prolonged bed rest, per se, has not been proven. On the contrary I find many advantages in permitting the patient with cardiomyopathy, after an initial period of observation and appropriate treatment if indicated, to engage in all moderate, normal activities as tolerated. Competitive sports, especially those demanding speed and endurance are interdicted. Syncope and sudden death have followed strenuous activity or acute intense emotional stress, and such activity and stress should be avoided. Surgical treatment may be indicated in the obstructive form of cardiomyopathy in which resection of hypertrophied septum may be undertaken for attacks of syncope or intractable angina pectoris not responsive to beta-adrenergic blocking agents such as propranolol (Inderal), or possibly prosthetic replacement of a mitral valve should be considered when associated mitral regurgitation appears to be responsible for refractory heart failure.

This symposium summarizes some of the important aspects of idiopathic cardiomyopathy but also indicates the gross deficiencies in our knowledge and understanding of this challenging group of diseases. It is hoped that contents of the symposium will help the clinician in his comprehension and clinical diagnosis and management of the cardiomyopathies, and will stimulate the investigator to close the gaps in our knowledge and resolve some of the persistent problems. Circulation is greatly indebted to the contributors and expresses its appreciation to them for participation in this symposium.

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CHARLES K. FRIEDBERG

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