The Cardiomyopathies—Current Perspectives

By Joseph K. Perloff, M.D.

SUMMARY
This paper is designed to provide a contemporary overview of primary myocardial disease. The cardiomyopathies are dealt with in the light of both pathophysiologic and etiologic classifications. A relatively simple diagnostic approach is based upon these classifications together with the clinical manifestations of the cardiomyopathies. The essential principles of the natural history are summarized, and treatment is dealt with in terms of specific curatives, general pharmacologic measures, and management of factors that modify, aggravate, or contribute to the development of primary myocardial disease.

... following the protracted course of scarlet fever, diphtheria, typhoid fever, et cetera, marked changes occur in the form of interstitial inflammation which appear to satisfactorily explain the heart injury ... Ludwig Aschoff, 1904

"CARDIOMYOPATHY" means "heart (cardio) muscle disease (myopathy)." When the basic or primary cardiac pathology resides in heart muscle, we can speak of "primary cardiomyopathy" or "primary myocardial disease." It follows that this variety of myocardial abnormality does not result from pre-existing or coexisting disease of other cardiovascular structures (valves, coronary arteries, systemic arterioles, etc.), which is either absent altogether or functionally unimportant. If the etiology of the cardiomyopathy is unknown, the designation "idiopathic cardiomyopathy" or "idiopathic primary myocardial disease" is appropriate. If the etiology is known, the cardiomyopathy should be so designated.

For many physicians, the clinical diagnosis of primary myocardial disease is one of exclusion. However, much has been learned since Mattingly established primary myocardial disease as a nosologic entity 13 years ago.1 Current understanding of the cardiomyopathies generally permits their recognition to be approached just as directly as other cardiac diagnoses. It begs the question to say that certain alternatives must first be eliminated. Of course this is so, but such is the case with many diseases that are not merely diagnosed by exclusion.

Primary myocardial disease is best understood within the framework of some type of orderly grouping. Accordingly, classification has been approached from two points of view: (1) pathophysiologic, i.e., how the myocardium is affected in terms of structural and functional derangement, and (2) etiologic, i.e., the causes or presumed causes of the myocardial abnormalities. Concomitant consideration of both of these issues puts us in position to deal more intelligently with the clinical manifestations, natural history, and management. These classifications are appropriate for 1971. Time will undoubtedly dictate changes.

Pathophysiologic Classification
The pathophysiologic varieties of primary cardiomyopathy include the following alone or in combination: hypertrophic, hyperkinetic, obstructive, congestive, and restrictive. For practical purposes, left ventricular or biven-
tricular involvement is, with rare exception, always present. Hypertrophic cardiomyopathy implies an increase in left ventricular free-wall thickness, which may initially express itself clinically as uncomplicated hypertrophy with little or no functional impairment. Hyperkinetic cardiomyopathy means that the left ventricle contracts at an inappropriately fast rate. When the left ventricle is both hypertrophic and hyperkinetic the stage is set for obstructive cardiomyopathy, which has also been designated idiopathic hypertrophic subaortic stenosis, or muscular subaortic stenosis. Accordingly, obstructive cardiomyopathy is said to exist when a hypertrophic, hyperkinetic left ventricle develops a true left ventricular-aortic systolic gradient. Similar obstruction to right ventricular outflow may coexist. Congestive cardiomyopathy means that the essential clinical expression of the disorder is failure of the heart as a pump. The degree of failure may vary from subtle on the one hand to the advanced congested circulatory state of biventricular failure on the other. Restrictive cardiomyopathy indicates that both ventricular filling and contraction are impaired, as in constrictive pericarditis. The ventricles do not distend adequately in diastole despite high filling pressures, so the rate and degree of fiber shortening (and the volume and rate of systolic ejection) are reduced. Whether the impairment of ventricular contraction is inherent in the disease state or merely a reflection of impaired diastolic distention is unknown and functionally irrelevant.

The fact that the foregoing pathophysiologic patterns clinically overlap should not obscure their conceptual value. We can surely understand that some patients with hypertrophic cardiomyopathy develop congestive heart failure, some with congestive cardiomyopathy have hemodynamic evidence of myocardial restriction, and some with hypertrophic left ventricles are also hyperkinetic or both hyperkinetic and obstructed.

**Etiologic Classification**

An etiologic classification of primary myocardial disease is shown in table 1. In constructing this table, I have attempted to achieve a balance between the inherent value of relatively few categories and the oversimplification that ignores meaningful differences among closely related groups. For example, metabolic and infiltrative cardiomyopathies are listed separately; even though a number of metabolic disorders involving the myocardium are infiltrative, there are some infiltrative disorders that are not metabolic. Postpartum cardiomyopathy is still essentially "idiopathic," but the designation at least removes us one step from total ignorance and serves to direct investigative interests, as shown in Dr. Rahimtoola's article in this symposium. Furthermore, no etiologic classification should be taken to mean that only one cause is necessarily responsible for heart-muscle disease in a single patient. On the contrary, the development and natural history of cardiomyopathy may well depend upon a number of variables acting together.

**Idiopathic cardiomyopathy** merely means that at the time the myocardial disease is recognized its provoking cause or causes cannot be identified. Nevertheless, we can make some progress by determining the pathophysiologic pattern into which the cardiomyopathy falls. Idiopathic congestive cardiomyopathy is conceptually—and therapeutically—a different problem from hyperkinetic, hypertrophic, obstructive, or restrictive cardiomyopathy. Moreover, a given pathophysiologic category cannot help but make one consider etiologies that are believed to be responsible for such a pattern.

### Table 1

**Etiologic Classification**

<table>
<thead>
<tr>
<th>Number</th>
<th>Classification</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Idiopathic cardiomyopathy</td>
</tr>
<tr>
<td>2</td>
<td>Postpartum cardiomyopathy</td>
</tr>
<tr>
<td>3</td>
<td>Familial cardiomyopathy</td>
</tr>
<tr>
<td>4</td>
<td>Inflammatory cardiomyopathy (myocarditis)</td>
</tr>
<tr>
<td>5</td>
<td>Toxic cardiomyopathy</td>
</tr>
<tr>
<td>6</td>
<td>Metabolic cardiomyopathy</td>
</tr>
<tr>
<td>7</td>
<td>Nutritional cardiomyopathy</td>
</tr>
<tr>
<td>8</td>
<td>Infiltrative cardiomyopathy</td>
</tr>
<tr>
<td>9</td>
<td>Cardiomyopathy associated with heredofamilial degenerative neuromyopathic diseases</td>
</tr>
</tbody>
</table>
Postpartum cardiomyopathy is a term applied to idiopathic primary myocardial disease initially recognized in the puerperal period. By definition, patients with postpartum cardiomyopathy have no evidence of heart disease prior to pregnancy and no detectable cause of cardiac disease at the time they present. Some authors include women who develop cardiac failure in the last month of pregnancy or the first 5 months after delivery (see p 964). Others include only those women in whom cardiomyopathy appears between the second and twentieth postpartal weeks in order to eliminate, insofar as possible, occult preexisting heart disease that becomes overt during the stress of labor and delivery. Although there is little doubt that idiopathic congestive cardiomyopathy may be temporarily related to the end of gestation, the nature of the relationship is by no means clear. It is interesting in this regard that pregnancy has recently been shown to enhance the susceptibility of the myocardium of mice infected with encephalomyocarditis virus.

Familial cardiomyopathy implies recurrence of primary myocardial disease within a kinship. All disorders classified as familial cardiomyopathies are not necessarily the same. Idiopathic congestive or restrictive cardiomyopathies are seldom familial, whereas positive family histories are much more common in idiopathic hypertrophic cardiomyopathy, especially when obstruction to left ventricular outflow coexists. In fact, hypertrophic cardiomyopathy and hypertrophic obstructive cardiomyopathy may occur in different members of the same family. In addition, cardiomyopathy is well known in heredofamilial neuromyopathic diseases (see below).

Inflammatory cardiomyopathy (myocarditis) can be either infectious or noninfectious. It is sometimes possible to associate acute myocarditis with a specific etiology, but it is usually impossible to relate chronic myocarditis to a known cause. Accordingly, patients with chronic myocarditis typically present as idiopathic cardiomyopathy (usually congestive), since evidence of the provoking cause has long since disappeared.

Myocarditis associated with infectious diseases has been ascribed to direct tissue invasion (Coxsackie B virus), to toxins elaborated by an organism (diphtheria), or to an immune response (rheumatic fever). All types of infectious agents—viral, bacterial, rickettsial, spirochetal, parasitic, and fungal—have been associated with myocardial inflammation. However, viruses are the most common cause of primary infectious myocarditis in the United States. Many types have been incriminated but, as Dr. Abelmann indicates in his essay "Virus and the heart" (p 950), few seem to be clinically important in terms of prevalence, notably the enteroviruses and influenza. It is also important to point out that acute myocarditis, although potentially dangerous, is more often than not clinically occult and either vanishes altogether or presumably presents years later as chronic idiopathic cardiomyopathy.

Immunologic or autoimmune mechanisms have been postulated as causes of some types of "idiopathic" myocarditis. Such theories stem in part from the following lines of reason. The beta-hemolytic streptococcus, through an immune response, is known to cause myocarditis which, once established, can become self-perpetuating even after the infectious organism has vanished. Antibodies to heart muscle have been detected in almost two thirds of patients with the carditis of active rheumatic fever. Perhaps other infections (especially viral respiratory) disappear after initiating myocarditis through an immune response. A number of investigators have dealt with this theory but without providing evidence that it is so.

Heart-muscle antibodies have been found in idiopathic cardiomyopathy but far less often than in patients with miscellaneous cardiac diseases. Nor is there evidence that such antibodies are pathogenetically important.

The idea that an immune mechanism causes myocardial inflammation also applies to noninfectious myocarditis. Inflammatory disease of the myocardium is well known in the context of systemic disease of connective
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Nutritional cardiomyopathies are characteristically congestive and may stem from specific metabolic defects, such as thiamine deficiency in the polished-rice diet of Oriental beriberi. In 1951, Gillanders described a nutritional cardiomyopathy believed to result from the unbalanced high-carbohydrate, low-protein diet of the adult Bantu. Kwashiorkor, a disease of protein malnutrition in African children, is occasionally accompanied by an ill-defined degenerative cardiomyopathy.

Infiltrative cardiomyopathies are chiefly restrictive (occasionally congestive), and may be caused by either metabolic or nonmetabolic disorders. Hemochromatosis is a metabolic disease characterized by excessive deposition of iron in the tissues, including the myocardium. Gargoylism—from the cardiovascular point of view—can be considered a heredofamilial metabolic cardiomyopathy associated with diffuse infiltration by cells filled with mucopolysaccharides. The glycogen-storage disease of Pompe is a metabolic cardiomyopathy of infancy associated with massive myocardial infiltration with glycogen. Fabry's disease is a rare metabolic disorder in which extensive glycolipid deposits are present in many organs, including the heart. Nonmetabolic infiltrative cardiomyopathies include amyloidosis (restrictive), sarcoidosis (congestive cardiomyopathy in addition to cor pulmonale and conduction and rhythm disturbances), and neoplastic infiltration (restrictive or congestive).

Three heredofamilial neuromyopathic diseases associated with cardiomyopathy are progressive muscular dystrophy, myotonic muscular dystrophy, and Friedreich's ataxia. Myocardial involvement is especially common and serious in classic pseudohypertrophic Duchenne's progressive muscular dystrophy and in Friedreich's ataxia.

Clinical Diagnosis

The clinical diagnosis of primary myocardial disease is best approached in three steps:
Table 2

Chief Clinical Manifestations

<table>
<thead>
<tr>
<th>Asymptomatic</th>
<th>Symptomatic</th>
</tr>
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<tbody>
<tr>
<td>—</td>
<td>Chest pain</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>Pericardial</td>
</tr>
<tr>
<td>Palpitations or cerebral symptoms (giddiness, dizziness, syncope)</td>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td>Ischemic</td>
<td>Pulmonary</td>
</tr>
<tr>
<td>Embolism</td>
<td>Systemic</td>
</tr>
<tr>
<td>Sudden death, circulatory collapse</td>
<td></td>
</tr>
<tr>
<td>Left ventricular or biventricular failure</td>
<td>Left ventricular hypertrophy</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td>Hyperkinetic left ventricle and systemic arterial pulse</td>
</tr>
<tr>
<td>Hypokinetic (restricted) ventricles with high venous pressure</td>
<td></td>
</tr>
<tr>
<td>Midsystolic (rapid ejection, obstruction)</td>
<td>Tachyarrhythmias</td>
</tr>
<tr>
<td>Holosystolic (A-V-valve regurgitation)</td>
<td>Conduction defects</td>
</tr>
<tr>
<td>Third and fourth heart sounds (gallop rhythm)</td>
<td>Atrioventricular</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>Bundle-branch block</td>
</tr>
<tr>
<td>Pericarditis</td>
<td></td>
</tr>
<tr>
<td>Electrocardiogram</td>
<td></td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td></td>
</tr>
<tr>
<td>Left axis deviation</td>
<td>Infarct pattern</td>
</tr>
<tr>
<td>Nonspecific repolarization abnormalities</td>
<td>Normal</td>
</tr>
<tr>
<td>Normal</td>
<td>Cardiomegaly without pulmonary venous congestion</td>
</tr>
<tr>
<td>X-ray</td>
<td>Cardiomegaly with pulmonary venous congestion</td>
</tr>
<tr>
<td>Abnormal left ventricular silhouette</td>
<td>Normal</td>
</tr>
</tbody>
</table>

(1) recognition of cardiomyopathy as the essential disease category, (2) identification of the pathophysiologic type, and (3) etiologic classification.

Recognition of primary myocardial disease is simplest when comparatively young, normotensive individuals present with cardiomegaly, left ventricular hypertrophy, tachyarrhythmias, conduction disturbances, or heart failure, without a prior cardiac history and without clinical evidence of acquired valvular heart disease, congenital heart disease, or disease of the coronary arteries, lungs, or pericardium. Such individuals initially may be asymptomatic. On the other hand, cardiac failure may be sudden and unremitting, or tachyarrhythmias dangerous and rapidly fatal before heart failure has had time to develop.

More specific clinical manifestations are shown in table 2.

The uncomplicated pathophysiologic categories are often readily suspected in the context of the history, physical signs, electrocardiogram, and X-rays, but at other times characterization and differential diagnosis demand hemodynamic investigation. The distinction between hyperkinetic and hypertrophic cardiomyopathy with and without obstruction may require physical and pharmacologic interventions in the catheterization laboratory. Special concern attends the differential diagnosis between restrictive cardiomyopathy (a nonsurgical disease) and noncalcific constrictive pericarditis, which may be amendable to surgical relief. Although thoracotomy has often been preformed in order to
make this distinction, coronary arteriography has recently been employed to define the ventricular epicardium and estimate the thickness of overlying pericardium.5

In considering the pathophysiologic categories, we should understand that some patients with primary myocardial disease, especially those with asymptomatic idiopathic cardiomegaly, may have hearts that clinically function normally or nearly so. Furthermore, the basic pathophysiologic disturbance may, during its natural history, assume features of other categories: hyperkinetic hearts become hypertrophic, hypertrophic hearts fail, and restricted hearts produce circulatory congestion.

Once the presence and pathophysiologic type of primary myocardial disease have been satisfactorily established, we next turn attention to the etiologic categories themselves (table 1). It is useful to begin with the question, "Given the pathophysiologic type of cardiomyopathy with which we are dealing, which of the etiologic categories is most likely to apply?" Any pathophysiologic type can be idiopathic. However, congestive cardiomyopathy is likely to be inflammatory, toxic, metabolic, nutritional, or postpartal; restrictive cardiomyopathy is likely to be infiltrative; hypertrophic cardiomyopathy with or without obstruction is more likely to be familial; cardiomyopathy presenting as an isolated arrhythmia is likely to be inflammatory. After the etiologic priorities have been settled, each relevant category should receive specific attention in planning diagnostic evaluation. For example, consideration of acute inflammatory cardiomyopathy (myocarditis) requires questioning regarding recent respiratory infection, attempts to recover virus from throat or stool, viral serology, laboratory tests for specific collagen diseases, etc. It should also be borne in mind that an occasional patient presents with what appears to be uncomplicated self-limited acute pericarditis (perhaps Coxsackie B) that is followed by the development of congestive cardiomyopathy or noncalcific pericardial constriction which may be difficult to distinguish from restrictive cardiomyopathy.16, 25 Consideration of congestive cardiomyopathy caused by toxins or nutritional deficiencies requires a careful history regarding alcohol ingestion, drug administration, and dietary habits. Restrictive cardiomyopathy may be due to amyloidosis, which can be specifically diagnosed by appropriate biopsy.10 Chest pain warrants pointed comment since symptomatic coronary artery disease warns against a diagnosis of cardiomyopathy. It is therefore important to know that typical "ischemic" pain can occur in patients with primary myocardial disease, especially hypertrophic cardiomyopathy with or without obstruction.5, 12 Furthermore, infarct patterns may appear in the electrocardiograms in the absence of chest pain.26 Chest pain in cardiomyopathic patients may also result from pulmonary embolism or (at least initially) from pericarditis.

Etiologic evaluation must not fail to consider the effect of several contributory factors acting together. The nutritionally deficient chronic alcoholic who contracts a Coxsackie B infection in a hot humid environment is more likely to develop overt cardiomyopathy than a well-nourished nonalcoholic who contracts the same infection during the pleasant weather of early spring.

Natural History

The natural history of primary myocardial diseases, like any general disease category that encompasses a variety of pathophysiologic and etiologic considerations, is bound to be variable, but certain principles can nevertheless be extracted.25

Acute primary myocardial disease may be clinically occult, disappearing with little or no residual, or may theoretically present years later as idiopathic cardiomyopathy, although the link between acute myocarditis and chronic cardiomyopathy in man is yet to be firmly established. Alternatively, acute cardiomyopathies may present as either dangerous arrhythmias or as progressive or remittent heart failure ending in death.25 Chronic primary myocardial disease—irrespective of pathophysiologic type—may remain stable for
years but ultimately progresses, either slowly or rapidly, with congestive heart failure as the common denominator. Either the acute or chronic course may be terminated by sudden death or may be punctuated by pulmonary or systemic embolism.25

**Treatment**

Ideally, early diagnosis with identification of a specific etiology should set the stage for best therapeutic results. Beriberi heart disease is a case in point. However, current therapeutic measures for patients with primary myocardial disease, whether acute or chronic, are seldom specific curatives even when a cause is identified. Nevertheless, therapeutic measures should be related to cause insofar as possible. If a heavy ethanol drinker has cardiomyopathy, abstention is clearly desirable whether alcohol is believed to be the major cause or not.20 Nutritional deficiencies should be corrected even if a specific (e.g. thiamine) deficiency cannot be identified. Systemic diseases (such as hyperthyroidism) that may be contributory or causative should be appropriately controlled. Dr. Abelmann mentions myocarditis associated with certain infectious diseases that are amendable to antibiotic treatment (tetracycline for psittacosis, primary atypical pneumonia, or lymphogranuloma venereum) (see p 954).

Pharmacologic management involves four considerations, namely: congestive heart failure; rate, rhythm, and conduction disturbances; thromboembolic complications; and antiinflammatory principles. The use of digitals, diuretics, and sodium restriction is, as a rule, beneficial in treating the congestive heart failure of both acute and chronic cardiomyopathies. Concern with increased sensitivity to digitalis,25 especially in acute myocarditis, speaks for the use of rapidly acting, rapidly excreted preparations such as digoxin without loading doses and with comparatively small maintenance doses. Serious tachyarrhythmias and conduction disturbances should not simply be managed by standard pharmacologic regimens, but instead should be handled in intensive-care units until control has reduced the threat of sudden death. Anticoagulants should be used both for and in anticipation of pulmonary embolism (chronic congestive heart failure) and for systemic embolism from mural thrombi (especially during cardioversion).

The use of antiinflammatory (immunosuppressive) agents has been controversial but some guidelines can be recommended. Dr. Abelmann calls attention to the deleterious effects of corticosteroids on experimental Coxsackie B and Chagasie myocarditis, and legitimately concerns himself with the possibility of similar response in man. Nevertheless, certain patients believed to have noninfectious myocarditis have experienced substantial improvement following corticoids. It is prudent to be cautious and selective, but, when one is confronted with uncontrolled myocarditis that is clearly threatening a patient’s life, corticosteroids can be employed as potentially useful antiinflammatory drugs.

The management of contributory or aggravating causes in patients with primary myocardial disease has received considerable attention, and justifiably so. An increased burden on an already diseased heart is clearly undesirable. A number of factors are relevant in this regard, namely, exercise, obesity, environmental stress, heat and humidity, hypoxia, respiratory infections of bacterial etiology, coexisting systemic disease, and preexisting cardiovascular disease. Limitations of physical activity during the acute phase of myocarditis and in the presence of overt congestive heart failure seem to be appropriate based on simple hemodynamic considerations alone. In addition, exercise has been shown to increase myocardial proliferation of cardiotropic strains of Coxsackie virus in inoculated mice. Dr. George Burch has observed that otherwise intractable heart failure in chronic congestive cardiomyopathy may respond to prolonged bed rest.7,27 Care must be taken in assigning the degree and duration of physical limitations believed to be appropriate for a given patient. An asymptomatic individual with idiopathic cardiomegaly may require only moderate restriction. A class 4 patient with congestive cardiomyopathy

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may respond only to bed rest for a year or more. Prolonged bed rest, though widely applied, is still a debated issue. Furthermore, we lack precise information regarding the cardiocirculatory effects of protracted physical immobilization in normal man.

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References
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