Primary Myocardial Disease

By NOBLE O. FOWLER, M.D., AND MOSCHE GUERON, M.D.

Definition

The term primary myocardial disease refers to a variety of cardiac enlargement which is of unknown cause and frequently leads to cardiac dilatation, congestive heart failure, and finally to death. There are a number of synonyms. The disorder is also called idiopathic myocardial hypertrophy, myocardiopathy, cardiac hypertrophy of unknown cause, and, especially in Great Britain, cardiomyopathy. In some centers the term "myocardosis" is used, although myocardosis includes, in addition to primary myocardial disease of unknown origin, certain specific etiologic diseases of the heart such as beriberi, amyloidosis, hemochromatosis, and von Gierke's disease.

Etiology

The cause of primary myocardial disease, as indicated in the definition, is unknown. In the University of Cincinnati series, patients with this disorder were from 18 months to 68 years of age at death. Because of the wide age distribution it seems likely that this descriptive term embraces a heterogeneous group of disorders rather than a single entity. Although specific etiologies cannot be assigned, the following possibilities merit more than casual consideration.

1. Heredity. In many instances, there are several patients with primary myocardiopathy in a single kinship, although in only two instances was this relationship observed in the University of Cincinnati group. Ventricular outflow tract obstruction, causing aortic stenosis on the left and pulmonic stenosis on the right may occur in both nonfamilial and in the familial forms of primary myocardial disease.3

2. Infections. It has been postulated that the clinical picture of primary myocardial disease may follow viral myocarditis, or may be caused by diphtheria or toxoplasmosis. In our series of patients with histologic studies of the myocardium who now number 29, no patient was included whose myocardium showed significant accumulations of inflammatory cells. However, focal areas of myocardial fibrosis were found in 18 patients of this group. It is not impossible that these areas of scarring represent the end result of myocardial inflammation. One patient observed since our last report in 19622 is of especial interest in this regard. This patient was a 27-year-old white man who was admitted to the hospital with the clinical features of pericarditis and cardiac tamponade. After relief of cardiac tamponade, he rapidly developed myocardial dilatation, to be followed by death after 6 months of intractable heart failure. At necropsy there was cardiac enlargement without evidence of myocardial inflammation and thus the patient could be included in our group of patients with primary myocardial disease. However, there was obliteratorive adhesive pericarditis. In this patient it seemed highly likely that there was an initial inflammation involving both pericardium and myocardium, which was rapidly followed by myocardial dilatation and failure. Unfortunately, studies for viral disease were not made in any of our patients.

3. Alcoholism. Evans4 suggested that alcohol leads to a specific form of cardiomyopathy. Eight patients of the 23 in our last report had a history of alcoholism. Although alcohol alone may not cause a specific form of myocardial degeneration, an occasional patient is admitted to the hospital with unexplained myocardial failure after a prolonged bout of alcoholism. The congestive heart failure responds rapidly to treatment and the
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patient recovers in a few weeks without residual evidence of heart disease.

4. Beriberi heart disease, and other vitamin deficiencies. Somewhat more indirectly related to alcoholism is the problem of beriberi heart disease. It has been postulated that in some instances primary myocardiopathy is the result of beriberi heart disease. Patients with beriberi heart disease at the University of Cincinnati hospitals have almost always been alcoholics and have had clinical evidence of either thiamine or niacin deficiency. The study of Rowlands and Vilter, and that of Griffith, failed to demonstrate that beriberi would result in specific permanent pathologic alterations of the myocardium. Burch and Walsh reviewed the evidence and were unable to conclude that deficiencies of niacin, pyridoxine, ascorbic acid, or of vitamins A, D, or E could be clearly related to human myocardial disease. However, in dogs pyridoxine deficiency may lead to cardiac insufficiency and death.

5. Nutritional cirrhosis of the liver. In some series the prevalence of primary myocardial disease has been high in patients with nutritional cirrhosis of the liver. One group described 12 instances of idiopathic cardiac enlargement in 108 patients who died of portal cirrhosis. In our series of 28 patients, only three had evidence of nutritional cirrhosis and two had fatty livers. Thus the abnormal myocardial metabolism described by Zobl and co-workers in nutritional cirrhosis may be related to the myocardial enlargement in a few of our patients, but would not account for the majority.

6. Postpartum myocarditis. Some authorities have postulated a specific form of myocardial disease during the postpartum state, beginning most commonly between 5 and 30 days after parturition. It remains uncertain as to whether or not pregnancy itself is the cause of the disorder or is only coincidental or a precipitating factor in a patient who already has a myocardial abnormality. Postpartum myocarditis was a possibility in only one patient in our autopsied group. Three other patients still survive with cardiac enlargement persisting for a year or more after the onset of congestive heart failure in the postpartum period.

7. Subendocardial fibroelastosis. Focal subendocardial fibroelastosis was found in the hearts of some of our patients, principally over the papillary muscles. It was not disproportionate to that commonly seen in longstanding congestive heart failure with cardiac dilatation. In no instance did the hearts resemble the adult variety of subendocardial fibroelastosis. The adult form of subendocardial fibroelastosis is extremely rare, but several patients with primary myocardial disease come to autopsy each year at the University of Cincinnati hospitals.

8. Autoimmune disease. This is a possibility, but as yet is without substantial proof.

9. Myocardial metabolic disorder. Studies of myocardial metabolism have shown occasional negative balances of pyruvate and lactate and at times myocardial glycolysis.

Pathologic Data

Our experience comprises 29 patients from whom anatomic data are available. Three were studied by exploratory thoracotomy. In our group of 26 patients studied at autopsy, the heart weights were above normal in each. Mural thrombi were found in 14 patients; five had systemic embolism; and six, pulmonary embolism. Left ventricular thickness was increased in all patients save four; in these the left ventricle was dilated. The right ventricle was increased in thickness in approximately half the necropsied patients. There were focal areas of myocardial fibrosis in 18 patients (fig. 1); only one had a large area of scarring, and none had extensive subendocardial fibroelastosis.

Diagnosis

The diagnosis of primary myocardial disease is usually suggested after excluding the more common causes of congestive heart failure. The problem has been thoroughly discussed by Mattingly. At the University of Cincinnati hospitals most patients with this disorder when first seen are considered to have one of four more specific varieties of heart

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disease: (1) rheumatic heart disease, (2) pericardial disease, (3) hypertensive cardiovascular disease, (4) coronary artery disease, usually termed arteriosclerotic heart disease or ASHD. We should like to consider briefly how each of these diseases may be simulated by primary myocardiopathy.

Rheumatic Heart Disease

Patients with primary myocardial disorders are often thought to have rheumatic heart disease because they commonly have systolic cardiac murmurs. These systolic murmurs are generally related to incompetence of the mitral valve caused by left ventricular dilation, or to incompetence of the tricuspid valve caused by right ventricular dilation. These murmurs are pansystolic, the mitral murmur being loudest at the cardiac apex and referred to the left axilla. They may be as much as grade IV (of VI) in intensity. The tricuspid murmur is usually loudest at the left lower sternal edge or midway between this area and the cardiac apex. It is characteristically increased with inspiration but not always so, and is often accompanied by systolic pulsations of the neck veins and of the liver. As a rule, the systolic murmurs of these patients tend to become louder when the congestive heart failure and cardiac dilatation increase; the murmurs tend to become softer, or often disappear when the congestive heart failure and cardiac dilatation improve in response to treatment. This change in murmurs with treatment is often a valuable point in distinguishing the disorders in question from rheumatic heart disease in which murmurs often become louder with improving cardiac compensation.

Other features may cause confusion with chronic rheumatic valvular heart disease. Very commonly there is an early diastolic ventricular gallop and at times a short apical diastolic rumbling murmur, thus simulating mitral stenosis. The apical diastolic murmur may result from a combination of atrial and ventricular gallop sounds.14 When heart failure is present, a ventricular gallop rhythm is almost always found.13 It is not infrequent to find both ventricular and atrial gallops. Too, the left atrium is often enlarged fluoroscopically and may displace the barium-filled esophagus posteriorly and even elevate the left main stem bronchus. One such patient in our group had a persistent loud apical systolic murmur and was for years thought to have rheumatic heart disease. At autopsy the mitral valve ring was so stretched that it admitted four fingers. The left atrium was huge but there was no rheumatic mitral disease. On chest roentgenogram Kerley B lines may be found above the costophrenic angles thus increasing the likelihood of a misdiagnosis of rheumatic mitral disease. Aortic ejection systolic murmurs8 and late aortic systolic murmurs15 may result from obstruction to left ventricular outflow by hypertrophied muscle. Thus, congenital or rheumatic aortic stenosis is suggested. Only one patient in our series had a murmur of aortic insufficiency. Fluoroscopic demonstration of aortic or mitral valve calcification is virtually diagnostic of rheumatic heart disease.

Pericardial Disease

These patients present several features that may suggest pericardial disease, either constrictive pericarditis or pericardial effusion with cardiac tamponade. The neck veins may be very prominent, distended, and pulsating. Inspiratory distention of the neck veins and

Figure 1

prominent x and y descents may be found. If the response to treatment for congestive heart failure is poor, persistent elevation of the venous pressure may suggest pericardial disease. The heart sounds may be faint. The radiologic contour of the heart may suggest pericardial disease as does the often feeble cardiac pulsation at cardiac fluoroscopy. In our group, four of 15 patients showed at fluoroscopy generalized diminution of cardiac pulsation. Pericardial disease may also be suggested by an abnormal inspiratory decrease of systemic arterial blood pressure, i.e., paradoxical pulse. A palpable paradoxical pulse was observed in only one patient in our autopsied group. In a few instances, we have found it necessary to employ cardiac scanning or angiocardiography (figs. 2 and 3) to exclude pericardial effusion in these patients. In most instances, the eventual decline in venous pressure which follows the customary treatment for congestive heart failure will make it clear that the patient has myocardial rather than pericardial disease.

**Hypertension**

Many patients in our group were at one time believed to have hypertensive cardiovascular disease. Five of 23 patients had at one time a diastolic blood pressure of 100 mm Hg or more.\(^2\) As a rule, hypertension was present only during bouts of congestive heart failure and was of only a few weeks’ duration. In some patients with primary myocardial disease the diastolic blood pressure becomes temporarily elevated during congestive heart failure, but declines to normal after subsidence of heart failure. Since the pathologic changes in the myocardium are not specific in primary myocardial disease, the pathologist must rely principally upon the clinical measurements of blood pressure to exclude hypertension. The pathologist is aided by histologic study of the kidneys. As an additional measure to exclude hypertension, we have required the absence of nephrosclerosis or significant inflammatory disease of the kidney. It is probable that many of these patients in the past have been incorrectly
labeled as hypertensive cardiovascular disease even after autopsy.

**Coronary Artery Disease**

Many patients with primary myocardial disease are quite advanced in years. In our group of 29 patients with histologic studies of the myocardium, eight were fifty or older. Thus, despite the absence of a history of angina pectoris or of myocardial infarction, it is common for these patients during life to receive the label of coronary artery disease as the cause of their otherwise unexplained heart failure. At the University of Cincinnati hospitals, the label of “ASHD” (arteriosclerotic heart disease) is commonly used. The diagnosis of coronary disease is often suggested because the electrocardiogram may show QS complexes in leads II and III as the result of abnormal left axis deviation, or may show QS complexes in the right precordial leads suggesting myocardial infarction (fig. 4). Pruitt and co-workers have reported three patients with idiopathic myocardial disease whose electrocardiograms demonstrated abnormal Q waves in the left precordial leads, with striking resemblance to the electrocardiogram of myocardial infarction. None of the patients in our group had an entirely normal electrocardiogram. Other abnormalities that might suggest coronary artery disease were left bundle-branch block in six, and atrial fibrillation, which developed in 10 of the 29 patients. Although not observed in our autopsy series, complete atrioventricular block and ectopic ventricular arrhythmias have been reported by others. Only three patients in our series had gross evidence of coronary atherosclerosis and in none of these was there significant narrowing of the lumen of the coronary arteries. However, one patient had coronary embolism originating from a left ventricular mural thrombus.

The diagnosis of primary myocardial disease is difficult to make with certainty. The possibility of valvular heart disease must be excluded by observation of the change in murmurs after treatment for cardiac dilatation and failure, and, where necessary, by measurement of pressure gradients across the mitral or aortic valve by means of cardiac catheterization. Right heart catheterization in five patients of our group revealed a low cardiac output with elevation of pulmonary wedge pressure and of right atrial pressure, consistent with biventricular failure. As a rule, pulmonary wedge pressure exceeds right atrial pressure by 10 mm Hg or more, in distinction from constrictive pericarditis. In one patient the diastolic pressure in the right

Figure 4

*Electrocardiogram of a 27-year-old man who died of primary myocardiopathy after 6 months of congestive heart failure. The limb leads demonstrate abnormal left axis deviation. There are small to absent R waves in leads V₂ through V₅ suggesting healed myocardial infarction. There was no myocardial infarction at autopsy.*

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ventricle was equal to one third of the systolic pressure, a relationship similar to that described in constrictive pericarditis. The right heart catheterization studies are not of specific value, since the hemodynamic pattern found in primary myocardial disease is not diagnostic and may at times resemble that of constrictive pericarditis. Systolic pressure gradients between the main left ventricle and its outflow tract may be found when the hypertrophied muscle obstructs the left ventricular outflow tract and a similar obstruction may be demonstrated in the right ventricle. In such instances, cardioangiography may be required to delineate the site of obstruction. Hypertensive cardiovascular disease can usually be excluded by examination of the ocular fundi and careful analysis of the patient's blood pressure record. In primary cardiomyopathy, the blood pressure is normal or is elevated only in relation to bouts of congestive heart failure. Pericardial disease can usually be excluded by changes in heart size, pulsation, and venous pressure after treatment for heart failure. On occasion angiocardiography or cardiac scanning following the intravenous injection of carbon dioxide or radioactive iodinated serum albumin is required to evaluate the thickness of the pericardium. Coronary artery disease is difficult to exclude with certainty. We have not employed coronary arteriography for this purpose. It seems unlikely that treatment would be sufficiently altered by a diagnosis of coronary disease so obtained to warrant the added risk. In our experience, patients who have considerable cardiac dilatation with prolonged survival after the onset of congestive heart failure without evidence of diabetes mellitus, hypercholesteremia, angina pectoris, or myocardial infarction are more likely to have idiopathic myocardial hypertrophy than coronary artery disease.

Even if the above disorders can be excluded, there remains the problem of the distinction between primary myocardial disease and other forms of myocardial disease. Kline and Saphir have shown that myocarditis may produce a similar picture of chronic congestive heart failure during life and at gross autopsy, and that fever and increased sedimentation rate may not always be present. One 51-year-old woman at the Cincinnati General Hospital was thought to have primary myocardial disease as the cause of congestive heart failure of 7 years' duration. However, microscopic examination of the myocardium revealed evidence of active rheumatic myocarditis, despite normal heart valves. Sarcoidosis of the myocardium may produce congestive heart failure. As a rule there are enlarged lymph nodes in the neck and mediastinum and often there is pulmonary infiltration. Occasionally sarcoidosis is almost entirely confined to the myocardium; liver biopsy may be of diagnostic value. Cardiac amyloidosis may be very difficult to distinguish from primary cardiomyopathy, especially in the patient over fifty. Liver, tongue, gum, or rectal biopsy may be of value. Serum electrophoresis and occasionally the Congo-red test may be contributory. If the patient has evidence of hepatic cirrhosis or diabetes mellitus the possibility of hemochromatosis must be borne in mind. Patients should be examined carefully for evidence of Friedreich's ataxia or of progressive muscular dystrophy, which may be associated with myocardial involvement. Myocardial degeneration may occur with myotonic muscular dystrophy. Diseases of collagen, such as dermatomyositis, scleroderma, and disseminated lupus erythematosus must be kept in mind. Metastatic neoplastic disease involving the myocardium is usually obvious. In an infant or young child, von Gierke's disease, an anomalous left coronary artery, myocarditis, or subendocardial fibroelastosis may be difficult to exclude. In a few instances we have resorted to exploratory thoracotomy and myocardial biopsy to confirm the diagnosis; others have employed needle biopsy of the myocardium. Since the treatment for the disorder in question is not specific, it seems unlikely that such measures are warranted as a routine, unless another disorder which can be treated more specifically is under serious consideration.

Clinical Course

Of the 29 patients in our present series,
only four were females. Most of these patients were collected from the Cincinnati Veterans Hospital, thus the sex distribution is not representative of the general population. In three patients the disorder was known to begin before adult life. Nineteen patients were white, and 10 were Negro. The duration of the disease from the time of the first diagnosis covered a wide range. One patient developed rapidly progressive heart failure and died within 6 months after his first symptoms. Many patients, however, responded repeatedly and well to treatment for heart failure before the final episode. In our group, 13 patients survived 5 years or more after the onset of heart failure; six survived 10 years or more, and one patient survived 26 years. Systemic and pulmonary embolism were common and presumably often related to the frequent mural thrombi. Fourteen of the 26 autopsied patients had mural thrombi; five had systemic embolism; and six had pulmonary embolism.

**Treatment**

The treatment of primary myocardial disease is somewhat unsatisfactory in that it cannot be expected to achieve a cure. The treatment may be considered under the following categories: (1) management of congestive failure, (2) prolonged bed rest, (3) the use of anticoagulants, (4) the use of adrenal steroids, and (5) surgical operation for relief of outflow tract obstruction. The use of these measures has been discussed elsewhere in this Symposium.

**References**

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