Primary Myocardial Disease

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During the past few years we have observed several patients who demonstrated cardiac enlargement and clinical symptoms and signs of congestive heart failure without convincing evidence of hypertension, coronary artery disease, or valvular heart disease. When death occurred, sometimes after years of chronic congestive heart failure, autopsy revealed none of the usual causes of heart disease. These patients were considered to have primary myocardial disease. In this paper is described a group of 17 such patients who have been subjected to postmortem examination at the Cincinnati General Hospital, the Cincinnati Veterans Hospital, or the Cincinnati Children's Hospital, and one patient from personal observation at the Brooklyn Hospital, Brooklyn, New York. Five of the patients were personally examined by one of the authors, and rightsided heart catheterization was performed in four of the patients.

Material and Methods

The diagnostic files of the Departments of Pathology of the Cincinnati General Hospital, Veterans Hospital, and Children's Hospital were searched for cases coded as myocardosis,* heart failure of unknown etiology, or as primary myocardial disease.† The files were examined for the last 30, 7, and 9 years respectively.

The patients who were included in this study were required to meet certain clinical and pathologic criteria. The specific clinical criteria for the selection of patients were (1) the presence of cardiac enlargement and congestive heart failure, except in two patients with nutritional cirrhosis; (2) the absence of sustained diastolic hypertension of 100 mm. Hg or more; (3) the absence of clinical or laboratory evidence of such renal disease as glomerulonephritis or chronic pyelonephritis or of collagen disease such as lupus erythematosus or scleroderma; (4) the absence of significant anemia, avitaminosis, thyrotoxicosis, or myxedema.

In all 18 patients autopsy protocols and microscopic sections were reviewed. In general the criteria for inclusion of patients in this group from the pathologic viewpoint was the finding of unexplained cardiomegaly. The specific pathologic criteria employed for excluding accepted causes of cardiac hypertrophy were (1) absence of significant coronary artery disease (three patients with a moderate degree of coronary arteriosclerosis were included in whom the arteriosclerotic process did not cause significant narrowing of the vessel lumen); (2) absence of other disorders commonly related to myocardial hypertrophy, such as intracardiac shunts or valvular disease; (3) absence of significant pulmonary parenchymal or vascular disease, such as severe pulmonary emphysema, severe pulmonary fibrosis, pulmonary sarcoidosis, or chronic recurrent pulmonary embolism; (4) absence of renal disease that could be related to clinically unidentified hypertension, such as glomerulonephritis, nephrosclerosis, or severe pyelonephritis; (5) absence of amyloidosis, collagen diseases, such as lupus erythematosus, dermatomyositis, or scleroderma, hemochromatosis, subendocardial fibroelastosis, or myocardiitis.

The material used for pathologic study was routinely fixed in either Zenker's acetic acid, 5 per cent solution, or 10 per cent buffered formalin. One to eight sections of cardiac muscle were available for study in each patient (one in one case, two in four cases, three in three cases, four in six cases, six in three cases, and eight in one case). The routine stain employed was hematoxylin and eosin. Special stains were performed on appropriate material: (1) fat stains—Sudan IV (10 patients); (2) periodic acid Schiff digested and undigested—all but no. 12 and no. 15; (3) crystal violet stain for amyloid (all but no. 12 and no. 14); (4) Van Gieson and trichrome stains (all but no. 12 and no. 14); (5) elastic tissue stains (all but no. 12 and no. 14). In addition the skeletal muscles were examined microscopically in seven instances.

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*Mycardosis: A term employed to describe significant enlargement of the heart unexplained by inflammatory, vascular, neoplastic, or neuromuscular disorders.

†Primary myocardial disease is a subdivision of myocardiosis but excludes beriberi, amyloidosis, hemochromatosis, and Von Gierke's disease.
PRIMARY MYOCARDIAL DISEASE

Results

Clinical Observations

Eighteen patients were found to meet the clinical and pathologic criteria. These patients comprised the group referred to in this paper as primary myocardial disease. Fourteen of the patients were male, 11 were Caucasian, and seven were Negro. The youngest was 18 months and the oldest 68 years of age. Six were below the age of 40, six were from 40 to 49 years of age, and six were from 60 to 68 years of age. One of the female patients (no. 4, table 1) had several uneventful pregnancies. Congestive heart failure appeared for the first time several weeks after her last confinement.

A family history was available in only 13 of the entire group. Nine reported no family history of cardiac disease. Two (no. 9 and no. 13, table 1) gave a history of arteriosclerotic heart disease in close relatives, and one (no. 7) rheumatic fever in a younger member of the family. Only one (no. 12) reported similar heart disease in a brother.

No patient showed clinical evidence of pellagra, peripheral neuritis, or peripheral signs of high output failure. Three patients were reported to be heavy consumers of alcoholic beverages. Three other patients admitted a mild or moderate alcoholic intake.

In four patients (nos. 6, 8, 11, and 17) casual readings of blood pressure were elevated at some time during the period of observation. Patient 17 was treated for 2 years for congestive heart failure by a private physician. During this period of time a single record of 170 mm. Hg systolic pressure was reported. The blood pressure was always normal during the 7 subsequent years of observation. Patient 11 was observed for 15 years because of congestive heart failure and cardiomegaly beginning at the age of 31. After 2 years of observation, a casual blood pressure reading of 160/130 mm. Hg was reported. The blood pressure returned to normal after treatment for congestive heart failure and remained normal for the ensuing 13 years. Several months before he died he was seen during a bout of severe congestive heart failure. The blood pressure was elevated twice at 180/110 and 160/100. After treatment the pressure returned to normal levels a month later and remained normal until death. Patient 8 was first admitted because of subarachnoid bleeding. The blood pressure on the day of admission was 160/130 mm. Hg. The blood pressure returned to normal on the next day and remained normal throughout the subsequent year of observation for nutritional cirrhosis. His second and last admission 13 months later was because of congestive heart failure; his blood pressure was normal at this time. Patient 6 was also admitted because of subarachnoid bleeding and congestive heart failure. The blood pressure was elevated but subsequently returned to normal. He remained normotensive during a 2-year period of observation and treatment for congestive heart failure.

No patient gave a history of a febrile illness related to the onset of his disease. Sixteen subjects recalled the onset of their illness: shortness of breath, dyspnea, and dependent edema were the usual initial symptoms. Two of these patients were first seen with symptoms of frank pulmonary edema or paroxysmal nocturnal dyspnea. Six patients succumbed within 2 years after signs of congestive failure developed. In one the duration of congestive heart failure was not known, and in nine the duration was between 3 and 16 years. In two of the patients (nos. 9 and 14) with nutritional cirrhosis, the existence of heart disease was not suspected prior to necropsy. Ten of these 18 patients were hospitalized because of severe congestive heart failure on at least two occasions, and eight had been in the hospital only once. All but two patients had elevated venous pressure on each admission.

Twelve of the 18 patients had at some time systolic murmurs at the cardiac apex, aortic area, or left sternal border, graded two to four (grade-range one to six) in intensity. Extensive description of the murmurs was not given, nor was attention directed to their relation to respiration or to their duration.
Table 1
Pathologic Data in Eighteen Patients with Primary Myocardial Disease

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Heart wt.</th>
<th>Rt. Atrium</th>
<th>Lt. Atrium</th>
<th>Lt. Ventricle</th>
<th>Stomach (mm.)</th>
<th>Lt. Ventricle</th>
<th>Pericardium</th>
<th>Thrombi</th>
<th>Other diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. B. 1</td>
<td>440*</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>7</td>
<td>2</td>
<td>normal</td>
<td>lt. vent.</td>
</tr>
<tr>
<td>M. M. 2</td>
<td>468</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3.5</td>
<td>10</td>
<td>normal</td>
<td>none</td>
</tr>
<tr>
<td>G. P. 3</td>
<td>565</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>4</td>
<td>20</td>
<td>normal</td>
<td>none</td>
</tr>
<tr>
<td>V. H. 4</td>
<td>470</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>4</td>
<td>14</td>
<td>normal</td>
<td>lt. vent.</td>
</tr>
<tr>
<td>P. Y. 5</td>
<td>580</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>4</td>
<td>15</td>
<td>550 ml. transudate</td>
<td>rt. atrium</td>
</tr>
<tr>
<td>C. F. 6</td>
<td>700</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>7</td>
<td>20</td>
<td>100 ml. transudate</td>
<td>lt. vent.</td>
</tr>
<tr>
<td>N. B. 7</td>
<td>625</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>5</td>
<td>14</td>
<td>normal</td>
<td>rt. atrium, lt. vent.</td>
</tr>
<tr>
<td>G. A. 8</td>
<td>575</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>4</td>
<td>20</td>
<td>normal</td>
<td>none</td>
</tr>
<tr>
<td>P. G. 9</td>
<td>425</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>5-6</td>
<td>15</td>
<td>normal</td>
<td>none</td>
</tr>
<tr>
<td>H. H. 10</td>
<td>675</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>not hyper-trophied</td>
<td></td>
<td>normal</td>
<td>none</td>
</tr>
<tr>
<td>O. M. 11</td>
<td>655</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>3</td>
<td>5-10</td>
<td>normal</td>
<td>lt. vent.</td>
</tr>
<tr>
<td>F. S. 12</td>
<td>440</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>5</td>
<td>18</td>
<td>-</td>
<td>both atra</td>
</tr>
<tr>
<td>W. M. 13</td>
<td>675</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>5</td>
<td>20</td>
<td>normal</td>
<td>rt. atrium</td>
</tr>
<tr>
<td>G. V. 14</td>
<td>430</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>4</td>
<td>14</td>
<td>normal</td>
<td>none</td>
</tr>
<tr>
<td>E. W. 15</td>
<td>500</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>4</td>
<td>14</td>
<td>normal</td>
<td>lt. atrium</td>
</tr>
<tr>
<td>J. H. 16</td>
<td>625</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>6</td>
<td>20</td>
<td>normal</td>
<td>none</td>
</tr>
<tr>
<td>E. C. 17</td>
<td>625</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>10</td>
<td>17</td>
<td>normal</td>
<td>rt. atrium</td>
</tr>
<tr>
<td>H. K. 18</td>
<td>825</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>hyper-hyper-trophied</td>
<td></td>
<td>normal</td>
<td>atrial</td>
</tr>
</tbody>
</table>

*Heart and lungs weighed together.

In three patients a diastolic rumbling murmur was heard in the mitral area; in two an early diastolic blowing murmur was localized at the left sternal border, during one of multiple admissions; these diastolic murmurs were not persistent. In four patients no murmurs were described; in eight a diastolic apical gallop rhythm was heard. As a rule, the gallop rhythm disappeared after intensive treatment for heart failure, to return during the next admission or shortly before the final illness. A significant paradoxical pulse was described once in one patient. Examinations of the ocular fundi were reported in 14 patients; 11 were described as normal. Two showed grade one and one showed grade two hypertensive changes, but none had hemorrhages or exudates. None of the patients had clinical evidence of thyrotoxicosis; none had a hemoglobin below 10 Gm. per 100 ml. of blood.

Serum protein values were available in
six patients; in only two was the albumin-globulin ratio reversed. The total protein values ranged from 5.3 to 7.2 Gm. per 100 ml. of blood, and the serum albumin values were between 1.3 to 3.65 Gm. per 100 ml.; only one patient had a serum albumin value below 2.5 Gm. per 100 ml. of blood.

Of the 18 patients, 16 had at least one electrocardiogram recorded and many had several during each admission. The electrocardiograms of three patients showed abnormal left axis deviation (mean QRS vector directed leftward beyond $-30^\circ$) and each of the three had electrocardiographic evidence of left ventricular hypertrophy. Three others had a mean QRS vector greater than $110^\circ$, indicating abnormal right axis deviation; only one of these showed suggestive evidence of right ventricular hypertrophy. Biventricular hypertrophy was suspected in one patient without abnormal axis deviation. Two patients showed a mean QRS axis of $-90^\circ$. Minor T-wave abnormalities were found in eight patients at some time during their illness. Only three patients of the entire group had definite low voltage of the QRS in the limb leads, but the QRS voltage was normal in the precordial leads. The low voltage QRS complexes in the limb leads were seen during severe congestive heart failure and disappeared with clinical improvement. Seven patients displayed chronic atrial fibrillation throughout the course of illness. Two others showed temporary first degree atrioventricular block, thought to be due to digitalis. In two patients ectopic atrial and nodal tachycardia and interference dissociation were observed while they were receiving digitalis.

Fifteen patients were examined radiologically on more than one occasion and in eight of these, cardiac fluoroscopy was performed; one had only a single radiologic examination. In no instance was there seen valvular or pericardial calcification, abnormal pulsations of the pulmonary artery, abnormally increased or decreased pulmonary vascularity, or paradoxical pulsation of the left ventricle. Four showed generalized diminution of cardiac pulsation. Pulmonary changes produced by congestion were common. Generalized enlargement of the cardiac silhouette was seen in all 15 patients. The left atrium was thought to be prominent in five patients. It was not otherwise possible to detect selective or predominant chamber enlargement. Kerley lines were found in only one patient (no. 3).

Right heart catheterization was performed in four patients. The data obtained were essentially the same in each of the four patients (table 2). The cardiac index was well below normal in the three subjects in whom it was calculated. The arteriovenous oxygen differences were considerably above normal values in all four subjects. The mean right atrial pressure and the right ventricular diastolic pressure were elevated in three patients; in the fourth patient right atrial pressure and right ventricular diastolic pressures were normal, suggesting right ventricular compensation at the time. The pulmonary arterial and wedge pressures were increased in the three patients in whom they were measured, suggesting left ventricular decompensation. The right ventricular pressure curve of patient 12 showed a high diastolic plateau but not a marked diastolic dip. The hemodynamic data were consistent with congestive heart failure involving both ventricles with a low cardiac output.

Venous angiocardioigraphy was performed in patient 1 in order to exclude pericardial effusion. An extremely dilated right ventricle and prolonged circulation time were noted. No shunts or other abnormalities were visualized. The left atrium and ventricle were not opacified.

Systemic arterial embolism was not recognized clinically in any of these patients. The patients were treated with the usual regimen for cardiac failure by restriction of activity, low-sodium intake, digitalis, and diuretics. Antibiotic agents were used in most of the patients; one patient received cortisone for several months with no beneficial effect. Sixteen patients died with intractable heart failure; one (no. 14) died with septicemia, and one (no. 9) in coma as a result of aspiration pneumonia; in three instances pulmonary em-
Table 2

Right Heart Catheterization Data in Four Patients with Primary Myocardial Disease

<table>
<thead>
<tr>
<th>Case no.</th>
<th>RA mean mm. Hg</th>
<th>RV mean mm. Hg</th>
<th>PA mean mm. Hg</th>
<th>PW mean mm. Hg</th>
<th>PAR dynes sec. cm.−2</th>
<th>Systemic arterial oxygen saturation (per cent)</th>
<th>O₂ consumption L./min./M²</th>
<th>CI L./min./M²</th>
<th>CO L./min./100 ml</th>
<th>A-V O₂ difference mm. Hg</th>
<th>BP mean mm. Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17.8</td>
<td>50/5-10</td>
<td>50/29</td>
<td>27</td>
<td>375</td>
<td>90.8</td>
<td>147</td>
<td>1.1</td>
<td>1.9</td>
<td>7.9</td>
<td>58</td>
</tr>
<tr>
<td>3</td>
<td>11.5</td>
<td>50/24</td>
<td>3.0</td>
<td>17</td>
<td>557</td>
<td>94.8</td>
<td>200</td>
<td>1.5</td>
<td>2.4</td>
<td>8.3</td>
<td>65</td>
</tr>
<tr>
<td>12</td>
<td>18</td>
<td>48/18</td>
<td>56/30</td>
<td>28</td>
<td>—</td>
<td>97.0</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>6.8</td>
<td>—</td>
</tr>
</tbody>
</table>

RA, right atrial pressure; RV, right ventricular pressure; PA, pulmonary arterial pressure; PW, pulmonary wedge pressure; PAR, pulmonary arteriolar resistance—dynes sec. cm.−2; CI, cardiac index—liters per minute per square meter body surface; CO, cardiac output—liters per minute; AV, arteriovenous; BP, systemic blood pressure.

Emboli culminated the disease. The correct diagnosis was suspected clinically in only three patients. The cause of heart failure was listed as unknown in four; myocarditis was suspected in four, and in the remaining patients of the group rheumatic heart disease, arteriosclerotic heart disease or "collagen disease" was suspected to be the cause of the congestive heart failure.

Pathologic Observations

In 15 of the 18 patients coronary arteriosclerosis was slight or absent altogether. In the remaining three patients coronary artery disease was of moderate degree but was considered to be insufficient to account for the striking cardiac hypertrophy seen.

Cardiac hypertrophy was present in each instance. Exclusive of the 1½-year-old girl the hearts varied in weight from 425 to 825 Gm. (table 1). Usually the right and left ventricles were proportionately enlarged. The cardiac chambers were generally symmetric and in 13 cases dilated. In the remaining five cases the state of dilatation was not commented upon by the prosectors.

Intracardiac thrombi were encountered in 10 of the 18 patients in the left ventricle and in the atria (table 1). Embolism was noted in eight patients. Pulmonary infarction had occurred in six instances; in three there was no evidence of thrombus formation on the right side of the heart. Systemic embolic infarction was recognized in three subjects: the kidney was involved in two and the spleen in one.

Changes in the endocardium were inconspicuous and endocardial sclerosis was minimal. The epicardium was also normal.

The myocardial consistency was not the same in all instances. In four cases it was described as flabby, while in three the myocardium was said to be firm. There was no apparent correlation between the consistency and the postmortem interval or the extent of myocardial fibrosis.

While some degree of myocardial fibrosis was a frequent finding, it was usually absent (fig. 1, patient 6) or of slight degree, and in only four cases was it considered to be moderate (fig. 2, patient 3). There was no apparent correlation with mural or intramyocardial thrombosis, cardiac size, duration of heart failure, or the number of such periods of failure. In only one of the four instances of moderate fibrosis was the coronary arteriosclerosis more than slight and in this case (no. 12) a moderate degree of scarring was noted.

Except for an occasional small cluster of lymphocytes microscopic evidence of inflammation was not encountered. This reaction was thought to be inconsequential and not...
indicative of significant acute or chronic myocarditis.

The individual muscle fibers were generally enlarged and there were only nonspecific associated alterations, seen as interstitial edema and vacuolization.2 The pericardium in two patients (nos. 3 and 5, table 1) contained a large quantity of clear fluid (900 and 550 ml. respectively) and in one additional patient there was a mild transudate.

In a single case (no. 3) there were large quantities of deposit that was PAS-positive and diastase-resistant within myocardial fibers—especially with a perinuclear location (fig. 3). In three others an occasional focus of a similar material was found. Special stains were otherwise noncontributory. Amyloid stains were negative in 16 cases and the connective-tissue technics served only to confirm the presence of the fibrosis recognized in conventionally stained sections. Occasionally elastosis was manifest (fig. 4) over the convex portions of papillary muscles. In only one patient (no. 11) was fatty degeneration evident. This appeared as vacuolization of the sarcoplasm in occasional fibers and stained with Sudan IV.

Examination of the skeletal muscles revealed no significant lesions. In one instance (no. 3) cardiac cirrhosis was striking. In one patient (no. 14) there was advanced nutritional cirrhosis, and in two others early nutritional cirrhosis was observed. In one patient a mild degree of fatty infiltration of the liver was seen and in another a marked degree of fatty change was noted.

Discussion

When seen during life, the patient with primary myocardial disease is often considered to have hypertensive cardiovascular disease, rheumatic heart disease, coronary artery disease, or pericardial disease.

Some of these patients may have transient diastolic hypertension, presumably because patients who develop congestive heart failure may have an associated increased systemic vascular resistance.3-7 In this study we have considered that the absence of sustained diastolic hypertension militates against a diagnosis of hypertensive cardiovascular disease. None of the patients in this study had grade three or four eye-ground changes, and none of them had nephrosclerosis, glomerulonephritis, or severe pyelonephritis at necropsy.

Both clinical and radiographic observations may suggest the presence of rheumatic heart disease. Many of these patients have cardiac murmurs, presumably resulting from cardiac dilatation during congestive heart failure. They may have systolic apical murmurs resulting from relative mitral incompetence or systolic murmurs closer to the left sternal border resulting from tricuspid incompetence. Occasionally diastolic gallop rhythms may be mistaken for a mid-diastolic murmur of mitral stenosis. The radiologic examination may also be misleading because disproportionate left atrial enlargement may be found. Another roentgen finding that may suggest rheumatic heart disease is the finding of Kerley lines. Usually, however, the decrease in the intensity of the murmurs with a response to treatment will cast a doubt on the diagnosis of rheumatic heart disease. This was well illustrated in one of our patients (no. 3, table 1), who had been considered for years to have rheumatic mitral valvular disease; however, the inconstant nature of his apical systolic murmur indicated that this was rather the result of cardiac dilatation.

Coronary artery disease is also difficult to
exclude clinically. None of the patients in our group had angina pectoris; however, some patients may have electrocardiograms suggestive of previous infarction in association with abnormal left axis deviation or with left bundle-branch block. Frequently coronary artery disease is diagnosed clinically in this group as a diagnosis of exclusion because of its greater incidence than that of primary myocardial disease.

In addition many patients in this group were suspected at one time of having pericardial disease. The extreme cardiac dilatation seen in many of these patients often suggests the possibility of pericardial effusion. Furthermore, the feeble pulsations of the dilated heart may suggest to the radiologist pericardial effusion; however, the response of the venous pressure, edema, and hepatomegaly to the treatment for heart failure usually eliminates the diagnosis of pericardial disease. Paradoxical systemic arterial pulse may also be seen in primary myocardial disorders and again raises the question of pericardial involvement. Because patients with primary myocardial disease may have very high right ventricular diastolic pressure, right heart catheterization studies may be of little help in the differential diagnosis of these two disorders. In one of our patients (no. 12, table 2) right ventricular diastolic pressure exceeded one third of the systolic pressure, raising the question of cardiac constriction. Angiocardiography may be of value in excluding pericardial effusion or increased pericardial thickness.

The clinical picture of chronic myocarditis may resemble that of idiopathic myocardial disease. Kline and Saphir described six patients with heart failure due to chronic myocarditis. The duration of heart failure in this group was relatively short, being from 5 weeks to 16 months in five instances but 4 years in the sixth patient. In each subject described by Kline and Saphir necropsy revealed some degree of myocardial inflammation that was largely interstitial and consisted principally of lymphocytes and histiocytes. This degree of inflammation was not seen in our patients. Other disorders that may affect the myocardium, such as hemochromatosis, gargoylism, and Marfan's syndrome, can usually be readily excluded by clinical examination. Von Gierke's disease and subendocardial fibroelastosis are more difficult to differentiate from the disorder under question, and the distinction may be impossible during childhood. At necropsy the deposition of glycogen in the heart muscle fibers in Von Gierke's disease and the endocardial sclerosis and fibroelastosis make these diseases easily separable from primary myocardial disease. In the 7-year period studied at the Cincinnati Veterans Hospital, when eight instances of primary myocardial disease were found, no instance of subendocardial fibroelastosis was discovered.

Within the last 15 years several papers dealing with primary myocardial disease have been published. Spodick and Littman reviewed the literature up to 1958 and gathered 72 reported cases, adding eight of their own. The disease occurred in relatively young adults with a rapid deteriorating course. Thirty per cent of the patients in this group were Negroes. Elster's group of 10 patients was also largely composed of young adults. Only one patient was older than 50, whereas in our series six patients of the 18 were beyond this age. In Elster's group six of 10 were Negroes; three of the 10 patients were female. Elster and Spodick stressed the
relatively short course of the disease. Physical findings were similar in both reports and the most consistent clinical features were cardiac enlargement and evidence of congestive heart failure. Elster and Spodick also emphasized strongly the frequent occurrence of intracardiac thrombi and embolic phenomena. Elster\cite{11} reported slightly elevated diastolic blood pressure in five of his 10 patients and related this elevation to heart failure. Spodick’s\cite{10} patients were normotensive. Our group of 18 patients differed in three respects: (1) there were more older patients in our group; (2) many patients in our group had congestive heart failure of long duration; and (3) there was a relatively low incidence of clinical systemic arterial embolism.

In the literature we could find only one description of right heart catheterization in a patient with idiopathic myocardial hypertrophy. This was reported in a discussion of Elster’s paper\cite{12} by Dickinson Richards. The data showed low cardiac output and slightly elevated pressures in the pulmonary artery as have been frequently found in individuals recovering from congestive heart failure.\cite{13} Baleshum, McCord, and Blount\cite{14} reported right heart catheterization in two patients believed to have chronic myocarditis. The cardiac outputs were low, with increased arteriovenous oxygen difference. In a recent survey Lynfield and associates\cite{15} reported hemodynamic findings in six children with idiopathic cardiomegaly and significant fibroelastosis. The hemodynamic data in our patients did not differ significantly from those described by Blount and Richards and were similar to those in a group of patients with chronic left ventricular failure recently reported by Selzer.\cite{13}

In general the pertinent gross pathologic features of primary myocardial disease are those of a marked, usually symmetric hypertrophy, dilatation of all cardiac chambers and the frequent finding of intracardiac thrombi. The consistency of the myocardium may or may not be flabby. The cardiac muscle at times appears paler than normal. Grossly obvious fibrosis may or may not be present: when present, it tends to be most severe in

**Figure 3**

Microscopic section of the myocardium from case 3. The perinuclear deposit of PAS-positive, diastase-resistant material is prominent. Such deposits have no apparent relation to the degree of fibrosis.

The heart weights in our patients (average 579 Gm.) were comparable to those found by Elster and associates.\cite{11} These authors recorded heart weights of 430 to 800 Gm. in 10 patients with cardiac hypertrophy of unknown etiology, the average weight being 575 Gm. In Levy and Von Glahn’s study\cite{16} heart weights were between 440 and 740 Gm. in 10 patients with idiopathic cardiac hypertrophy. Intracardiac mural thrombosis was noted in 10 of our 18 patients: the thrombi were in the ventricles, in the atria, and in atria and ventricles. The significance of such thrombosis is unknown. Elster and associates\cite{11} also reported a high incidence of mural thrombosis of seven out of 10 instances. As in our series, Elster and associates found no severe myocardial fibrosis in their patients; in their group the fibrosis was principally subendocardial and endocardial. On the other hand, Levy and Von Glahn\cite{16} found more extensive areas of necrosis and fibrosis in their patients but were unable to demonstrate any relationship of these lesions to those of mural thrombosis.

The mechanism of production of myocardial fibrosis in this disorder remains unknown. Some authorities believe that subendocardial elastosis, seen to a minor degree in some of our cases, is secondary to cardiac dilatation.\cite{17-19} It is probable that the degree of
dilatation in our patients was insufficient to produce more than the minor changes that were observed.

The significance of the PAS-positive material noted in one of our patients is uncertain. It is believed to be the same as the so-called basophilic degeneration.20 This is a relatively common phenomenon in older individuals but its abundance in a young person is unusual (fig. 3).

Pathologic changes in the liver not secondary to heart failure were found in five subjects. Two subjects had fatty livers and three had nutritional cirrhosis. The incidence of alcoholism was high in the group from which these patients were obtained, and these changes in the liver may be coincidental rather than etiologic for the heart disease.

The etiology of primary myocardial disease is uncertain. It is quite possible that the patients included in our study represent several different disorders. Hereditary, infectious, and nutritional factors deserve consideration as possible etiologic mechanisms. It has been reported that in some instances idiopathic myocardial hypertrophy occurs in several members of one family.21–24 Such a familial occurrence was observed in only one of our patients. The pathologic and clinical findings do not permit distinction between these cases and those in which there is clearly no family history of cardiac disease of a similar type.

One must consider the possibility that chronic myocarditis could be responsible for the cardiac hypertrophy in our patients.8,25 It is difficult to believe that an inflammatory process could account for the marked cardiac hypertrophy seen in our subjects in the absence of either an infiltration of inflammatory cells or extensive myocardial fibrosis. Our patients, unlike those with isolated myocarditis, showed occasional small clusters of lymphocytes but no other cellular exudate.

Several of the patients in our group were alcoholic, and one must consider whether alcoholism is a factor in idiopathic cardiac enlargement. Myocardial damage has been produced by alcohol experimentally.26 Gould27 mentions the "beer drinker's heart" in human subjects but related the pathologic changes to the state of nutrition. Some of our patients had idiopathic cardiac hypertrophy in childhood, thus eliminating alcoholism as a cause of heart disease in all of these patients. Recently Gillanders28,29 has proposed that malnutrition or vitamin deficiency is the basic responsible factor in some instances for cardiomyopathy in the African. Idiopathic cardiomegaly, however, has been observed in very well nourished patients. The experience gained from clinical and necropsy studies in prison and in concentration camps has shown that atrophic rather than hypertrophic hearts were the rule in severe malnutrition.30 One could also raise the question that some of these patients may have chronic beriberi heart disease. The studies of Rowlands and Vilter2 and of Griffith31 failed to demonstrate that beriberi would result in specific permanent pathologic alterations in the myocardium. Since four of our patients had nutritional cirrhosis of the liver, one must consider whether this could be directly or indirectly responsible for the myocardial hypertrophy and heart failure. Wuhrmann and others have suggested that protein deficiency may be responsible for cardiac abnormalities found in nutritional cirrhosis.10,28,29,32 There are many other factors, however, in nutritional cirrhosis that may be responsible for impairment of cardiac function: anemia, vascular shunts, high output hyperdynamic states, increased plasma volume, and vitamin deficiencies.32–37
PRIMARY MYOCARDIAL DISEASE

An increased incidence of idiopathic cardiomegaly in nutritional cirrhosis was found by Lusneth, Olmstead, and Abboud who described 12 instances of idiopathic cardiac enlargement in 108 patients dying of portal cirrhosis. These authors postulated that the cardiac enlargement was related to the increased cardiac output often found in portal cirrhosis.33, 34

One patient in our group of 18 (no. 4) developed congestive heart failure for the first time during the early postpartum period, raising the question of postpartum myocarditis.38-40 She did not show evidence of pulmonary embolism, which may explain some instances of postpartum heart disease as indicated by Burchell, nor did she have evidence of hypertension to explain the heart failure, which may explain others. Whether or not postpartum heart disease is an entity or represents a coincidental development of heart failure in a patient with antecedent idiopathic cardiac enlargement remains in doubt.

The mechanism responsible for the cardiomegaly in primary myocardial disease remains obscure. It is possible that in some instances the pathogenesis is related to primary functional metabolic myocardial impairments, with dilatation and subsequent hypertrophy. It is possible that a disorder of the energy production-release mechanism of the heart as a result of disturbance of an enzyme system with or without recognizable liver disease could be a mechanism producing cardiac enlargement and failure in some instances.

Summary

This study describes 18 patients from the University of Cincinnati Hospitals who died of congestive heart failure without clinical or pathologic evidence of a primary cause.

Clinical features. Their ages were from 18 months to 68 years at death. Fourteen were male and four female; 11 were white and seven were Negro. Seven patients had heart failure for 5 years or more; three had heart failure for over 10 years. Seven patients were alcoholic and three had nutritional cirrhosis. Transient mitral or tricuspid systolic murmurs and apical protodiastolic gallop rhythms were common. Atrial fibrillation was present in six patients. The electrocardiograms revealed abnormal left axis deviation in three and left bundle-branch block in two.

Right heart catheterization was performed in four of these patients and showed low cardiac output, increased arteriovenous oxygen difference, and elevation of pulmonary arterial, pulmonary wedge, right ventricular diastolic, and right atrial pressures.

Pathologic features. Heart weights were over 500 Gm. in 13 patients; all 18 had left ventricular hypertrophy. Mural thrombi were present in 10; six had pulmonary emboli and three had systemic arterial emboli. One patient had gross myocardial scarring; only two had small accumulations of inflammatory cells in the myocardium. Ten had focal increase of elastic tissue.

Primary myocardial disease may simulate coronary artery disease because of the abnormal electrocardiogram; it may simulate hypertensive heart disease because of elevation of diastolic blood pressure during heart failure in some patients; it may simulate pericardial effusion because of the poor cardiac pulsations, narrow pulse pressure, and paradoxical pulse. It may simulate rheumatic heart disease because of the apical systolic and diastolic murmurs, left atrial enlargement, and presence of Kerley lines. The cause is unknown. Only one patient in this group had a familial history of similar heart disease.

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