The results of transvenous endomyocardial biopsy can frequently be used to diagnose myocardial diseases in patients with idiopathic heart failure

Endomyocardial biopsies in 100 consecutive patients revealed a substantial incidence of myocarditis

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ABSTRACT Transvenous endomyocardial biopsy is an accepted method to evaluate cardiac transplant rejection, but the clinical diagnostic value of the technique for other forms of cardiac disease has not been established. We performed biopsies in 100 consecutive patients without significant complications. The pathologic diagnostic information obtained was judged to be useful to the clinician in 54 and not useful in 46 patients. In 74 patients with congestive heart failure of unknown etiology and a dilated heart, useful pathologic diagnoses included myocarditis, vasculitis, doxorubicin cardiomyopathy, and congestive cardiomyopathy. In most of the patients with biopsy findings of myocarditis there were no other clinical or laboratory findings indicating the presence of this disease, and the diagnosis of myocarditis would have been overlooked without a biopsy. In 26 patients in whom there was clinical evidence of constrictive or restrictive cardiovascular physiologic characteristics, useful biopsy diagnoses included radiation-induced cardiomyopathy, endomyocardial fibrosis, amyloidosis, or no myocardial disease; in the patients without myocardial disease thoracotomies were performed for constrictive pericarditis. Transvenous endomyocardial biopsy can provide clinically useful information in the evaluation of diseases of the myocardium.


TRANSVENOUS endomyocardial biopsy (TEB) has been accepted as an accurate method to clinically evaluate the status of cardiac transplant rejection. However, there is disagreement as to whether TEB is a useful technique in the clinical evaluation of other forms of heart disease. Nonoperative cardiac biopsy was introduced as early as 1956 and was initially performed with a transthoracic needle. In 1962 Konno introduced a transvenous biopsy catheter that allowed myocardial biopsy samples to be obtained more safely. Subsequently, studies performed with modifications of the Konno catheter demonstrated that small samples of endomyocardium could be obtained with considerable safety and reliability. However, a 1978 editorial reviewed the previous experience with TEB and concluded that myocardial biopsy was not useful to the clinician attempting to diagnose the appropriate diagnosis and treatment for an individual patient. These authors felt the technique was useful only in diagnosing and managing cardiac transplant rejection.

To answer the question regarding the clinical usefulness of TEB, we have critically reviewed the clinical data and that obtained by biopsy from the first 100 patients who underwent TEB at the Massachusetts General Hospital over the past 7 years. For each patient the myocardial biopsy information was considered along with the clinical problem and judgments were made as to whether the biopsy added significant, useful information to the care of that patient. Our data show that when TEB is combined with a complete cardiac clinical evaluation, TEB frequently provided diagnostic information that was of major help to the clinician.

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Methods

Clinical information. Hospital and/or office records of all patients were reviewed and the patients’ physicians were interviewed (by cardiologists J.E.P., I.P., or P.C.B.). Emphasis was placed on the reason for performing the biopsy and whether the results yielded important and/or useful clinical information that was of subsequent use in the management of the patient. Each patient was followed until a judgment could be made regarding the clinical utility of the biopsy information.

This study represents a consecutive series of the first 100 initial myocardial biopsies performed at Massachusetts General Hospital from 1975 to 1982. If a patient underwent a repeat biopsy, the data obtained was not included in this study since the diagnosis had already been determined based on results of the initial procedure.

All patients included in this study were either inpatients or seen in the outpatient clinic of Massachusetts General Hospital. All patients gave a complete history and underwent physical examination, chest x-ray, electrocardiography, and routine blood tests. In addition, most of these patients had further cardiac noninvasive evaluation by echocardiography and radionuclide-gated blood pool scintigraphy to evaluate cardiac size and function. Also, all patients underwent right heart catheterization and all patients with suspected coronary artery disease underwent left heart catheterization and coronary angiography to exclude coronary narrowing as a cause of cardiac dysfunction.

Technique of TEB. All biopsies were performed on the right-ventricular septum with the use of the Caves-Schultz transvenous biopsy forceps and from the right internal jugular vein.2 The techniques used were very similar to those described by Mason.2

Multiple biopsy specimens (usually three to five samples measuring 1 to 1.5 mm) were taken from each patient and the tissue was preserved in a 10% buffered formalin solution for light microscopy, a 2.5% buffered gluteraldehyde solution for electron microscopy, and frozen in an embedding solution for subsequent immunofluorescent studies. Initially, we also performed viral cultures of pieces of myocardial tissue from 20 consecutive biopsies; because these viral cultures were all negative, no subsequent biopsies were cultured. Routine light-microscopy stains were as follows: hematoxylin and eosin, Mason trichrome, Prussian blue, Congo red, periodic acid-Schiff, and Von-Giesen.

Pathologic evaluation. All of the light microscopic slides were reviewed by two cardiac pathologists (H.T.A. and J.T.F.). Frozen endomyocardial tissue was sectioned and stained with hematoxylin and eosin and toluidine blue. These frozen tissue tissues were obtained to maximize the number of biopsy pieces examined for pathologic changes and also to facilitate the interpretation of the immunofluorescent stain. Tissue used for electron microscopic examination was cut into 1 mm blocks and processed in the usual way. Plastic “thick sections,” 1 μm thick, were made of each tissue block and stained with toluidine blue. All results reported here are based on examination of histologic slides, frozen hematoxylin and eosin– and toluidine blue–stained sections, and plastic thick sections. Criteria used to make specific pathologic diagnoses were as follows.

Myocarditis. The unequivocal diagnosis of myocarditis was made in the presence of prominent interstitial inflammatory infiltration with mononuclear and/or polymorphonuclear cells and diffuse myocyte degeneration and necrosis. There were cases in which only one such focus was observed in a single piece, but there were other cases in which this change was evident throughout the sample, either diffusely or multifocally (figure 1). In no case was there significant myocyte hypertrophy or fibrosis indicative of a chronic process.

The second diagnosis of myocarditis, called “consistent with myocarditis,” was made if there was diffuse interstitial infiltration with mononuclear inflammatory cells, at least focal evidence of myocyte degeneration, and prominent interstitial edema. Rare biopsies showed foci of active focal interstitial fibrosis in association with myocyte degeneration. Samples showing replacement fibrosis, myocyte hypertrophy with bizarre nuclei, or endocardial fibrosis, even in the presence of occasional scattered inflammatory cells, were excluded from this category and diagnosed as consistent with congestive cardiomyopathy (see below).

Congestive cardiomyopathy. The microscopic changes that we considered suggestive of congestive cardiomyopathy consisted of endocardial thickening, prominent myocyte hypertrophy and atrophy, interstitial fibrosis, and foci of replacement fibrosis. These changes were felt to be consistent with the clinical diagnosis of congestive cardiomyopathy.1 5 Although these changes are clearly abnormal, by themselves they are not definitively diagnostic. As previously mentioned, if the changes of congestive cardiomyopathy were marked, the presence of an occasional inflammatory cell was not felt to warrant the diagnosis of myocarditis. Differentiation between this category (consistent with congestive cardiomyopathy) and nonspecific changes (see below) was based on a quantitative assessment by the pathologist of the severity of the pathologic changes evident in the biopsy. Mild changes were categorized as nonspecific whereas severe abnormalities were felt to warrant the diagnosis of consistent with congestive cardiomyopathy.

Loeffler’s endomyocarditis. Acute Loeffler’s endomyocardi- tis was diagnosed by the presence of acute myocarditis (with or without prominence of eosinophils) and blood eosinophilia (>1500 eosinophils/mm3). Biopsy specimens from patients with a clinical diagnosis of subacute or chronic Loeffler’s disease showed a change of endomyocardial fibrosis, i.e., thickening and fibrosis of endocardium extending into subjacent myocardi um.

Sarcoidosis. Criteria for the unequivocal diagnosis of sarco- dosis include the presence of nonnecrotizing granulomas. The sample from one patient, which showed evidence of systemic sarcoidosis, did not have granulomas, but showed diffuse histio- cytic and mononuclear cell myocardial infiltrates. This was judged to be consistent with sarcoïd involvement of the heart in a patient with evidence of systemic disease with sarcoidosis.

Amyloid deposition. Amyloid deposition was diagnosed by a positive Congo red stain with typical green birefringence under polarized light. The diagnosis was subsequently confirmed by a positive thioflavin-T stain and electron microscopic examination.

Doxorubicin cardiotoxicity. The changes attributed to doxorubcin have been described amply by Bristow et al.17; their criteria and classification were used.

Radiation cardiomyopathy. This diagnosis was made if the biopsy showed myocyte hypertrophy and vacuolar degeneration, marked interstitial fibrosis, endocardial fibrosis, and atypical interstitial fibroblasts and endothelial cells.

Scleroderma heart disease. The changes of scleroderma heart disease in the absence of coronary artery disease have been described.18 Patchy broad bands of replacement fibrosis of different ages was felt to be consistent with scleroderma heart disease.

Vasculitis. The diagnosis of vasculitis was made on classic pathologic grounds, i.e., the presence of inflammation in the vascular wall, fibrin deposition, and evidence of focal vascular wall necrosis.

Nonspecific or mild changes. These consisted of mild focal interstitial or mild focal replacement fibrosis, mild hypertrophy, and mild focal fibrous thickening of the endocardium.

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DIAGNOSTIC METHODS–MYOCARDIAL DISEASE

FIGURE 1. Histopathologic section from a transvenous endomyocardial biopsy showing changes judged to be pathologically diagnostic of myocarditis. There is scattered, prominent inflammatory cell infiltration with myocyte necrosis and degeneration and some interstitial fibrosis (hematoxylin and eosin stain × 300).

No diagnostic abnormality. This was the label given to myocardial biopsies that were found to be entirely normal.

Categorization of the effect of TEB on clinical outcome. After review of the indication for biopsy, clinical history, pathologic results of biopsy, and subsequent clinical course of each patient a judgment was made regarding the clinical usefulness of the TEB to the clinical outcome of the patient. TEB was judged to be clinically useful if the pathologic findings on biopsy provided one of the following: (1) Pathologic findings diagnostic of a specific disease. (2) Pathologic findings consistent with but not diagnostic of a certain disease. If a patient had a clinical syndrome consistent with a disease entity and the biopsy showed consistent findings, this was considered very strong evidence supporting the diagnosis of the disease being considered. (3) Pathologic findings not indicating a myocardial cause of restrictive or constrictive cardiovascular physiology and suggesting the need for thoracotomy and pericardiectomy.

TEB was judged to be not useful clinically if it did not provide any clinical diagnostic information.

Autopsy. Six patients died within 6 months of undergoing TEB and conventional postmortem examinations were performed. The pathologic findings of TEB were compared with postmortem results.

Results

Clinical indications for TEB. In the present series, all 100 patients demonstrated symptoms and/or signs of congestive heart failure that were of unclear etiology. To facilitate evaluation of these 100 patients, they have been divided into groups of those with dilated hearts (by chest x-ray or echocardiography) and those with normal or only mildly dilated hearts (table I). Although many of these patients demonstrated nonsustained ventricular arrhythmias, evaluation of the rhythm disturbance was not a primary indication for biopsy in any patient in this series. Seven patients demonstrated syncope as part of their clinical presentation but the specific indication for biopsy was to evaluate idiopathic congestive heart failure.

Complications of TEB. During the biopsy procedure in these 100 patients, two patients developed sustained
ventricular tachycardia that required electric cardioversion. No other complications occurred. Specifically, there were no episodes of right ventricular perforation, tamponade, pneumothorax, or heart block.

Pathologic findings on TEB. Table 1 lists the indications for TEB and the pathologic findings noted upon biopsy.

In 19 of the 100 patients, biopsy was felt to be diagnostic of (nine patients) or consistent with (10 patients) inflammatory myocarditis. The clinical characteristics of these 19 patients are listed in table 2. The mean age of this group was 45 years, with a range of 25 to 75. Nine were women and 10 were men. Myocarditis was one of the possible diagnostic considerations for most of these patients (17 of 19) before TEB. In all 19 patients, the presenting symptoms included dyspnea secondary to congestive heart failure. Other symptoms were chest pain (n = 5), palpitations (n = 2), profound fatigue (n = 2), near syncope (n = 1), edema (n = 1), and hemoptysis (n = 1).

The amount of time from onset of symptoms to evaluation with TEB is shown in table 3. The duration of symptoms in this series before biopsy ranged from ½ to 30 months, with a mean of 7 months.

The clinical presentation of myocarditis has been described to include a preceding influenza-like syndrome, fever, elevated erythrocyte sedimentation rate, and/or peripheral leukocytosis. Table 2 shows the frequency of observation of these signs and symptoms in our 19 patients with biopsy-diagnosed myocarditis. It is interesting to note that none of 19 patients had all four, and eight of 19 had none of these characteristics of myocardial inflammation. Furthermore, the erythrocyte sedimentation rate, considered a sensitive test for myocarditis, was elevated in only six of 15 (40%) patients with myocarditis in whom the test was performed.

In three patients, TEB revealed myocarditis as well as other myocardial disease (amyloidosis, hypereosinophilic endomyocardial fibrosis with eosinophilia, or vasculitis). In one patient (No. 7) myocarditis was found on TEB; on postmortem examination, myocarditis was found along with polyarteritis nodosa involving large muscular arteries.

As demonstrated in table 1, 74 patients presenting with a dilated heart and congestive heart failure had the following diagnosis found by TEB: vasculitis (n = 1), doxorubicin cardiomyopathy (n = 2), congestive cardiomyopathy (n = 16), and systemic sarcoidosis with cardiac involvement (n = 1) or scleroderma (n = 1). The pathologic changes were considered diagnostically important in patients with vasculitis and doxorubicin cardiomyopathy. In the patients with congestive cardiomyopathy, the pathologic changes were considered consistent with this clinical syndrome, but these pathologic changes are not distinctive enough to be diagnos-

### Table 1
Flow chart of the clinical indication, pathologic findings, and clinical usefulness of transvenous endomyocardial biopsy in 100 patients

| Congestive heart failure of unknown etiology with a dilated heart (n = 74) | Myocarditis (n = 19)* | Vasculitis (n = 1) | Doxorubicin cardiomyopathy (n = 2) | Congestive cardiomyopathy (n = 16) | Cardiac involvement with sarcoidosis (n = 1) or scleroderma (n = 1) | Radiation-induced cardiomyopathy (n = 5) | Endomyocardial fibrosis (n = 3) | Cardiac amyloidosis (n = 6) | Normal transvenous endomyocardial biopsy leading to exploratory thoracotomy and finding constrictive pericarditis (n = 3) | No pathologic diagnosis or nonspecific changes (n = 46) |
|-----------------------------|----------------------|------------------|-------------------------------|---------------------------------|-----------------------------|---------------------------------|----------------------------|-----------------------------|-----------------------------|-----------------------------|---------------------------------|
| Elevated ventricular filling pressures, normal or mildly dilated heart, and constrictive or restrictive physiology (n = 26) | Useful (n = 54) | Not useful (n = 46) | | | | | | | | | |

*Numbers in parentheses refer to the number of patients.

*Three patients had two diagnoses: one patient had amyloidosis and myocarditis, one patient had endomyocardial fibrosis with eosinophilic myocarditis, and one patient had vasculitis and myocarditis, so that the number of patients or indications totals 100 and the number of pathologic findings totals 103.
tically useful. They do, however, provide useful clinical information because they confirm the clinical diagnosis of congestive cardiomyopathy and help rule out other pathologic processes, e.g., myocarditis. Findings of granulomatous inflammation in the heart of a patient with known sarcoidosis and of bands of myocardial fibrosis in a patient with systemic scleroderma, although they do not indicate an absolute diagnosis, do provide the important evidence that a systemic process has involved the heart and accounts for the cardiac dysfunction.

Twenty-six patients with elevated ventricular filling pressures, normal or mildly dilated hearts, and constrictive or restrictive physiology on catheterization had the following diagnoses found by TMB: radiation-induced cardiomyopathy (n = 5), endomyocardial fi-

### TABLE 2
Clinical characteristics of 19 patients with transvenous endomyocardial biopsy evidence of inflammatory myocarditis

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Indication for TMB</th>
<th>Presenting symptoms</th>
<th>Duration from onset of symptoms to TMB (mo)</th>
<th>Preceding flu-like illness</th>
<th>Erythrocyte sedimentation rate (≤ 20 mm Hg)</th>
<th>Peripheral count (nl &lt; 1200 cells/mm³)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>35</td>
<td>F</td>
<td>Myocarditis vs CMP</td>
<td>Dyspnea, chest pain</td>
<td>1</td>
<td>no</td>
<td>no</td>
<td>28</td>
<td>15,200 Diagnosis: eosinophilic myocarditis</td>
</tr>
<tr>
<td>2</td>
<td>49</td>
<td>F</td>
<td>Myocarditis vs CMP</td>
<td>Dyspnea</td>
<td>5</td>
<td>no</td>
<td>no</td>
<td>11</td>
<td>11,500 A</td>
</tr>
<tr>
<td>3</td>
<td>71</td>
<td>F</td>
<td>Myocarditis vs CMP</td>
<td>Dyspnea</td>
<td>18</td>
<td>no</td>
<td>no</td>
<td>1</td>
<td>ND</td>
</tr>
<tr>
<td>4</td>
<td>29</td>
<td>M</td>
<td>Myocarditis vs CMP</td>
<td>Dyspnea, hemopothy</td>
<td>9</td>
<td>no</td>
<td>no</td>
<td>ND</td>
<td>5700</td>
</tr>
<tr>
<td>5</td>
<td>48</td>
<td>M</td>
<td>Possible myocarditis</td>
<td>Dyspnea</td>
<td>1</td>
<td>yes</td>
<td>yes</td>
<td>15</td>
<td>6800 Diagnosis: myocarditis and vasculitis</td>
</tr>
<tr>
<td>6</td>
<td>50</td>
<td>F</td>
<td>Possible myocarditis</td>
<td>Dyspnea</td>
<td>6</td>
<td>no</td>
<td>yes</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>7</td>
<td>43</td>
<td>M</td>
<td>Possible myocarditis</td>
<td>Dyspnea</td>
<td>4</td>
<td>yes</td>
<td>no</td>
<td>121</td>
<td>6800</td>
</tr>
<tr>
<td>8</td>
<td>42</td>
<td>F</td>
<td>Myocarditis vs CMP</td>
<td>Dyspnea</td>
<td>8</td>
<td>no</td>
<td>no</td>
<td>5</td>
<td>9400</td>
</tr>
<tr>
<td>9</td>
<td>75</td>
<td>F</td>
<td>Possible amyloidosis</td>
<td>Dyspnea</td>
<td>3</td>
<td>yes</td>
<td>yes</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>10</td>
<td>57</td>
<td>M</td>
<td>Myocarditis vs CMP</td>
<td>Near syncope, dyspnea, edema</td>
<td>24</td>
<td>no</td>
<td>no</td>
<td>52</td>
<td>4800</td>
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<td>11</td>
<td>67</td>
<td>M</td>
<td>Possible amyloidosis</td>
<td>Restrictive/constrictive physiology</td>
<td>30</td>
<td>no</td>
<td>no</td>
<td>4</td>
<td>6200 Diagnosis: myocarditis and amyloidosis</td>
</tr>
<tr>
<td>12</td>
<td>47</td>
<td>F</td>
<td>Myocarditis vs CMP</td>
<td>Dyspnea, chest pain, palpitations</td>
<td>3</td>
<td>no</td>
<td>yes</td>
<td>13</td>
<td>7600</td>
</tr>
<tr>
<td>13</td>
<td>26</td>
<td>M</td>
<td>Possible myocarditis</td>
<td>Dyspnea, chest pain, palpitations</td>
<td>8</td>
<td>no</td>
<td>no</td>
<td>2</td>
<td>ND</td>
</tr>
<tr>
<td>14</td>
<td>41</td>
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<td>Dyspnea</td>
<td>6</td>
<td>no</td>
<td>no</td>
<td>ND</td>
<td>9400</td>
</tr>
<tr>
<td>15</td>
<td>28</td>
<td>M</td>
<td>Myocarditis vs CMP</td>
<td>Dyspnea</td>
<td>½</td>
<td>no</td>
<td>yes</td>
<td>80</td>
<td>12,200</td>
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<tr>
<td>16</td>
<td>30</td>
<td>M</td>
<td>Myocarditis vs CMP</td>
<td>Dyspnea</td>
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<td>no</td>
<td>84</td>
<td>14,700</td>
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<tr>
<td>17</td>
<td>25</td>
<td>M</td>
<td>Myocarditis vs CMP</td>
<td>Dyspnea, fatigue</td>
<td>½</td>
<td>no</td>
<td>yes</td>
<td>5</td>
<td>9700</td>
</tr>
<tr>
<td>18</td>
<td>54</td>
<td>F</td>
<td>Myocarditis vs CMP</td>
<td>Dyspnea</td>
<td>3</td>
<td>no</td>
<td>no</td>
<td>20</td>
<td>11,400</td>
</tr>
<tr>
<td>19</td>
<td>35</td>
<td>F</td>
<td>Myocarditis vs CMP</td>
<td>Dyspnea, chest pain, fatigue</td>
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<td>no</td>
<td>yes</td>
<td>44</td>
<td>9600</td>
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<tr>
<td>Mean</td>
<td>45</td>
<td>9F</td>
<td>—</td>
<td>—</td>
<td>7</td>
<td>3/19 yes</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3 elevated</td>
<td></td>
</tr>
</tbody>
</table>

*A Elevated due to another disease.*

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brosis (three patients total; two of three had eosinophilia), and cardiac amyloidosis (n = 6). In all of these patients the pathologic findings were considered diagnostic. In three patients, TEB revealed nonspecific changes leading to a presumptive diagnosis of constrictive pericarditis; thoracotomy revealed constrictive pericarditis that was reversed by pericardial stripping. In two other patients a nonspecific biopsy result led to thoracotomy, but constrictive pericarditis was not found; these patients were believed to have restrictive physiologic characteristics that were possibly secondary to idiopathic restrictive cardiomyopathy.

Autopsy findings. Six of the 100 patients died and postmortem examinations were performed on their hearts. In all six cases the autopsy findings confirmed those found on endomyocardial biopsy. Diagnoses in these six patients were myocarditis (n = 2), radiation-induced cardiomyopathy, idiopathic congestive cardiomyopathy, amyloidosis, and a normal biopsy. In one of the patients with myocarditis, although the autopsy did confirm severe myocarditis, the patient was also found to have necrotizing vasculitis of the large coronary arteries.

Discussion

There is considerable disagreement regarding the diagnostic usefulness of myocardial biopsy. Since the introduction of the transvenous myocardial biopsy forceps in 1962 by Konno, there have been a number of series describing the pathologic characteristics of myocardial biopsies. In 1974 Caves et al. described the usefulness of TEB in the diagnosis of cardiac transplant rejection. Biopsy became the accepted method to follow cardiac allografts, and was believed to contribute significantly to the increased survival of heart transplant patients. More recently, TEB has been advocated as one method to evaluate anthracycline-induced cardiomyopathy to determine whether more chemotherapy can be safely administered.

However, the role of TEB in evaluating other forms of myocardial disease has been debated. In 1978 Olsen reported on a European study arguing that biopsy pathology provided confirmatory (or nonconfirmatory) information in the evaluation of hypertrophic and congestive cardiomyopathies. Also in 1978, an editorial reviewed the accumulated experience with myocardial biopsy and concluded that TEB provided little or no clinically diagnostic information for the clinician. These authors felt that the small sample size, the restricted area from which the biopsy was taken (right ventricular septum), and the nonspecific nature of the response of the heart to damage were all factors that contributed to the inability of TEB to provide useful clinical information. They concluded that, except in heart transplant patients, TEB was not diagnostic; they recommended biopsy of noncardiac organs or tissues for evaluation of infiltrative cardiomyopathies, e.g., amyloidosis.

In this study we have addressed the question of the diagnostic usefulness of TEB in a consecutive series of 100 initial patients. TEB was found to provide clinically useful information in 54 of 100 patients. These patients had already undergone extensive noninvasive and invasive cardiac evaluation, and TEB was used to answer relatively specific diagnostic questions. Clinically useful TEB findings fell into three categories: (1) Pathologic findings diagnostic of a specific disease entity, e.g., vasculitis, doxorubicin cardiomyopathy, radiation-induced cardiomyopathy, endomyocardial fibrosis, and cardiac amyloidosis. (2) Pathologic findings consistent with but not diagnostic of a specific disease, e.g., congestive cardiomyopathy and cardiac involvement with sarcoidosis and scleroderma. The pathologic findings in these disease entities are not distinctive or specific enough to warrant a definitive pathologic diagnosis; however, in patients with clinical syndromes and cardiovascular evaluations that suggest this disease, the TEB findings provide useful supportive evidence. Patients with TEB evidence of myocarditis were classified as belonging to one of the above categories depending on the strength of the hist-

<table>
<thead>
<tr>
<th>Pathologic finding</th>
<th>No. of patients Follow-up or comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac amyloidosis</td>
<td>6</td>
</tr>
<tr>
<td>Endomyocardial fibrosis</td>
<td>3 One patient had diagnosis confirmed at autopsy</td>
</tr>
<tr>
<td>(with eosinophilia, n = 2; without eosinophilia, n = 1)</td>
<td></td>
</tr>
<tr>
<td>Radiation-induced cardiomyopathy</td>
<td>5</td>
</tr>
<tr>
<td>Nonspecific or normal biopsy</td>
<td>12 Three patients had constrictive pericarditis at thoracotomy</td>
</tr>
<tr>
<td></td>
<td>Two patients underwent thoracotomy but no constrictive pericarditis was present; patients judged to have idiopathic restrictive cardiomyopathy</td>
</tr>
<tr>
<td></td>
<td>Seven patients did not undergo thoracotomy, thus no judgment can be made</td>
</tr>
</tbody>
</table>

TABLE 3 Pathologic findings from 26 patients with constrictive or restrictive physiology
topathologic findings (see Methods). (3) Pathologic findings were nonspecific or normal in a patient with restrictive or constrictive physiologic characteristics, suggesting constrictive pericarditis. Of the five patients in this category who underwent thoracotomy, three had their constriction relieved by surgery and two did not. The latter two were judged to have restrictive characteristics that were possibly secondary to idiopathic restrictive cardiomyopathy. In these two cases and in the 44 other patients who demonstrated nonspecific changes or who had normal biopsy results, TEB was judged not to provide useful clinical information.

We chose this pathologic categorization because certain diseases, e.g., endomyocardial fibrosis, demonstrated such characteristic histology that all samples seen were believed to be diagnostically useful. In other diseases, best exemplified by myocarditis, a range of histologic changes were seen from severe extensive myocardial inflammation with myocyte necrosis to diffuse inflammatory round-cell infiltration with minimal myocytolysis. With myocarditis, obvious and severe myocardial inflammation was categorized as diagnostic, definite but less severe inflammation was categorized as consistent with but not diagnostic of myocarditis, and scattered inflammatory cells in the presence of prominent chronic myocardial changes, i.e., severe hypertrophy, marked replacement fibrosis, and endocardial thickening, were termed not diagnostic of myocarditis. We have not found averaging the number of lymphocytes per high-power field (as suggested by Edwards et al.21) particularly helpful in making a definitive diagnosis of myocarditis. We agree with Fowles and Mason22 that myocarditis represents a continuum and that the amount or type of inflammation, myofiber destruction, and fibrosis must be considered in deciding whether myocarditis is present or not. Further follow-up will be required to determine if the recent pathologic categorization of myocarditis by Fenoglio et al.23 is applicable to our patients.

The 100 patients reported in this paper are a consecutive series of the first 100 in whom TEBs were performed at the Massachusetts General Hospital from 1975 to 1982. Massachusetts General Hospital is both a tertiary and primary care hospital. Other than being a general cardiovascular referral institution, there are no peculiar referral patterns to the hospital that would skew the diagnoses determined by TEB. The general diagnostic percentages in this study (table 1) can be considered representative of any tertiary care institution.

In addition to processing our TEBs for light microscopy, biopsies were also examined by electron microscopy and an immunofluorescent technique. For diagnostic purposes, electron microscopy was found to be useful in identifying doxorubicin cardiotoxicity19 and in confirming the diagnosis of amyloidosis. It was of limited diagnostic value in the other diagnostic categories described in this study. Immunofluorescent staining for deposits of immunoglobulin and/or complement has demonstrated positive staining in most patients with and in some patients without histologic myocarditis.24 Whether routine immunofluorescent staining provides additional clinically useful diagnostic information is at present unknown and will require further study and clinical follow-up.

One of the most interesting and clinically important findings in this study was that 19 of the 100 study patients had myocarditis. Although the diagnosis of myocarditis had been one of the diagnostic considerations before TEB in 17 of 19 of these cases, few of these demonstrated classic symptoms or signs of myocarditis. Myocarditis has been described as an acute illness characterized by fever, chest pain, heart failure, elevated erythrocyte sedimentation rate, and leukocytosis.19 Eight of our 19 patients with myocarditis had none of these characteristics except heart failure. Thus, some patients presenting with idiopathic heart failure will have myocarditis that cannot be accurately diagnosed without TEB. Our finding agrees with that in a recently study that found biopsy evidence of myocarditis in four of 34 (12%) patients presenting with congestive heart failure and a dilated heart.16 Recent evidence suggests that some patients with myocarditis may respond to therapy with prednisone and an immunosuppressive drug,25 so that documenting the presence of myocarditis and instituting anti-inflammatory therapy may result in functional cardiovascular improvement in some patients.

In patients with constrictive or restrictive physiology and a normal or mildly dilated heart, TEB can provide direct pathologic tissue evidence for the diagnosis of amyloidosis, endomyocardial fibrosis, or radiation-induced cardiomyopathy. In patients with a nonspecific biopsy result, the diagnosis of constrictive pericarditis, which would require thoracotomy for diagnosis and stripping, should seriously be considered. Our series (table 3) demonstrates that TEB is not infallible in making this differentiation between restrictive cardiomyopathy and constrictive pericarditis, but it provides considerable diagnostic help. Since pericardectomy is effective in relieving constrictive pericarditis, and since there are possibly effective therapies for hypereosinophilic endomyocardial fibrosis26, 27 and amyloidosis,28, 29 it is important to define these specific
diagnoses for their therapeutic and prognostic implications.

Although the major purpose of this report is to highlight the clinical usefulness of TEB, it is important to recognize several limitations of the technique. The biopsies obtained are small (1 to 2 mm) and taken from one area of the heart (the right ventricular septum). We obtained three to five biopsies from several areas of the septum to provide a representative sample of the histopathology, but nonetheless a very focal process could have been missed. In six hearts that were autopsied, the histopathologic characteristics of the sample and the whole heart were similar because the disease processes considered in this article were generally diffuse. If, for example, TEB were used to evaluate myocardial involvement in coronary artery disease, the small biopsies would not provide representative samples.

In one patient the limitations and capabilities of TEB technique were particularly apparent. In a patient with multisystem disease, TEB revealed myocarditis. At postmortem examination extensive myocarditis was found, but the TEB had missed the diagnosis of vasculitis of the large muscular coronary vessels. This patient had systemic necrotizing vasculitis with coronary vasculitis and concomitant myocarditis. Because the vasculitis was limited to large vessels in this patient, TEB missed his diagnosis. In another patient in our series, the diagnosis of vasculitis was made on myocardial biopsy because small vessels were largely involved. Such cases indicate the need to perform coronary angiography to diagnose large-vessel vasculitis, and TEB should be performed to diagnose small-vessel inflammation.

Based on our findings in these 100 patients, we would recommend the use of TEB in the following clinical situations: (1) Patients with a dilated heart and moderate-to-severe congestive heart failure that is of unclear etiology should be considered candidates for TEB if the clinician feels they would be candidates for anti-inflammatory therapy if myocarditis were diagnosed. (2) Patients with normal or mildly dilated hearts, elevated ventricular filling pressures, and results of catheterization suggesting a restrictive or constrictive process. Based on clinical findings (e.g., calcified pericardium) or the nature of the catheterization pressures,20 restrictive cardiomyopathy and constrictive pericarditis can usually be distinguished from one another. However, in patients in whom the differentiation cannot be made on clinical grounds or with catheterization pressures, TEB can provide useful diagnostic information. Our experience does not include any patients who underwent TEB to evaluate the cause of severe arrhythmias.16

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The results of transvenous endomyocardial biopsy can frequently be used to diagnose myocardial diseases in patients with idiopathic heart failure. Endomyocardial biopsies in 100 consecutive patients revealed a substantial incidence of myocarditis.

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