Human myocardial histologic characteristics in congestive heart failure

DONALD V. UNVERFERTH, M.D., JULIE K. FETTERS, B.S., BARBARA J. UNVERFERTH, M.S.,
CARL V. LEIER, M.D., RAYMOND D. MAGORIEN, M.D., ANTHONY R. ARN, B.S.,
AND PETER B. BAKER, M.D.

ABSTRACT The purpose of this study was to identify the histologic characteristics of human myocardium in congestive heart failure (CHF) by cellular hypertrophy, nuclear area, endocardial thickness, and percentage of fibrosis and to correlate histologic findings to cause, severity, and duration of disease. Right ventricular endomyocardial biopsies from 109 patients were quantitatively analyzed. Ten patients with normal cardiac history, physical examination results, and cardiac function served as the control group. The remaining patients were divided into the following groups: those treated with doxorubicin (n = 18), and those with chest pain with normal coronary arteries (n = 8), familial CHF (n = 3), CHF associated with myotonic dystrophy (n = 3), peripartal CHF (n = 2), valvular CHF (n = 9), alcohol-induced CHF (n = 13), postviral CHF (n = 6), or idiopathic CHF (n = 36). Linear regression analyses showed a strong correlation between cell diameter and nuclear area (r = .70, p < .001) and weaker correlations between amount of fibrosis and cell diameter (r = .30, p < .005) and fibrosis and nuclear area (r = .29, p < .005). Results of function studies and histologic measurements (e.g., echocardiographically measured change in the minor-axis dimension of the left ventricle with systole and cell diameter) correlated poorly (r = −.33, p < .005). Duration of dyspnea did not correlate with any histologic factor. Within the normal group there was a direct correlation of cell diameter with age (r = .67, p < .05). Analysis of covariance revealed that the doxorubicin-treated patients had significantly less cellular hypertrophy but more fibrosis than the other patients. In those with alcohol-induced CHF the opposite pattern of more hypertrophy and less fibrosis was observed. The idiopathic and valvular CHF groups did not differ from each other or from the other groups. The results of this study demonstrate that fibrosis and hypertrophy tend to be worse in patients with severe CHF and that some myocardial insults (especially that of doxorubicin) induce a characteristic response to the injury.

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THE MYOCARDIUM has a simple structure and a limited range of responses to a wide variety of insults. These responses include fibrosis and cellular hypertrophy. The pattern and severity of fibrosis and hypertrophy have been used with varying success to differentiate hypertrophic from congestive cardiomyopathy, but have not been used to characterize the various types of nonischemic congestive heart failure (CHF).

The endocardial biopsy procedure has facilitated the study of cardiomyopathy. Before the advent of heart biopsy procedures, study was confined to that of autopsy specimens. The results of these studies reflected
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absence of correlation of histologic changes with duration of dyspnea. It is hoped that this information can help in the understanding of the pathogenesis of CHF and possibly the cause of idiopathic cardiomyopathy.

Methods

Patient selection. Endomyocardial biopsy samples from 109 patients were evaluated. These patients comprised the 10 following groups. (1) Normal subjects (n = 10). These subjects had normal cardiovascular histories and physical examination results. In addition, results of noninvasive tests to determine systolic time intervals and of echocardiographic examinations were normal. Each of these subjects had had a tumor necessitating doxorubicin chemotherapy and had participated in a study in which serial endomyocardial biopsy procedures (including at baseline) were performed. Data obtained from the baseline biopsies are the control data in this study. The Human Research Committee of our institution approved the previous study and also approved of our use of the tissue for the present study. (2) Doxorubicin-treated patients (n = 18). These patients had received over 200 mg/m² of doxorubicin (mean = 400 mg/m²). Cardiac function test results at the time of biopsy ranged from normal to severely depressed (table 1). The biopsies were taken from 1 to 6 months after the last dose of doxorubicin. All patients had normal cardiac function before undergoing doxorubicin chemotherapy. (3) Patients with chest pain and normal coronary arteries (n = 8). These patients had normal systolic function and normal coronary arteries as determined by cardiac catheterization, but each had chest pain that mimicked angina. (4) Patients with familial CHF (n = 3). These patients had dilated congestive cardiomyopathy of undetermined cause. Each had two or more first-degree relatives with dilated congestive cardiomyopathy. (5) Patients with CHF associated with myotonic dystrophy (n = 3). The clinical findings in these patients were consistent with myotonic dystrophy and there was no other apparent cause of their CHF. (6) Patients with peripartum CHF (n = 2). These two patients developed heart failure within 1 month after the delivery of a child and there was no other apparent cause of their CHF. (7) Patients with valvular CHF (n = 9). All patients in this group had severe valvular disease necessitating mitral (in three) or aortic (in four) valve replacement or both (in two). Each of these patients was still in heart failure 3 months or longer after valve replacement surgery. Catheterization revealed normal coronary arteries and normal prosthetic function. (8) Patients with alcohol-induced CHF (n = 13). Each of these patients had a dilated heart with poor systolic and diastolic function (table 1) and a history of heavy alcohol abuse that included the consumption of greater than 1 pint of whiskey (or equivalent) per day for over 2 years. None of these patients had consumed alcohol in the 2 months before they underwent the biopsy procedure. (9) Patients with postviral CHF (n = 6). Each of these patients had had biopsy–documented inflammatory myocarditis (more than five inflammatory cells per high-power field, n = 4) and/or a rise of viral titers during an acute viral-like illness that included arthralgias and electrocardiographic changes followed by the development of heart failure (n = 3). The biopsied tissue used for this study was obtained at least 3 months after the acute episode. No inflammatory cells were present in the biopsy samples at the time of this study. (10) Patients with idiopathic CHF (n = 36). These patients had dilated cardiomyopathies not attributable to alcohol abuse, family history of heart failure, myocarditis, primary valvular disease, cancer chemotherapy, or exposure to other cardiac toxins and onset was not within 3 months of the delivery of a child. They fulfilled the criteria of the World Health Organization for the classification of idiopathic dilated cardiomyopa-
screen was marked with a 5 mm grid containing 264 cross-points. Three randomly selected fields were evaluated per biopsy for a total of 792 points. By the method of Weibel, each cross-point was evaluated to determine whether it lay over a heart muscle cell or over connective tissue. The percent fibrosis for each biopsy was derived from the formula:

\[
\% \text{ Fibrosis} = \frac{\text{Points overlying connective tissue}}{\text{Points over connective tissue + points over muscle}} \times 100
\]

Endocardial thickness was also measured at five equidistant areas on the endocardial surface of the biopsy and the average was obtained. The section at a right angle to the endocardial surface was used for the calculations in this article. The endocardium was defined as the distance from the right ventricular cavity surface to the myocardial cells. This area usually includes the true endocardium and some subendocardial connective tissue.

Two microscopists made the measurements and the error on repeated measurements was less than 5% in most cases. When interobserver error was greater than 5%, a third determination was made. The microscopists were blinded to the grouping of the patients.

**Statistical analysis.** Data from groups 2 through 9 were compared with those from the normal group by unpaired Student t test (table 1). Pearson’s correlation formula was used to correlate histologic factors with clinical hemodynamic or with other histologic factors for the combined groups and within single groups. The patterns of increasing fibrosis and cellular hypertrophy with worsening myocardial performance, as determined by the %ΔD, were compared among the groups by the analysis of covariance.

<table>
<thead>
<tr>
<th>Group No</th>
<th>Cell diameter (μm)</th>
<th>Nuclear area (μm²)</th>
<th>Endocardial thickness (μm)</th>
<th>% Fibrosis</th>
<th>%ΔD</th>
<th>PEP/LVET (%)</th>
<th>Ejection fraction (l/min/m²)</th>
<th>Cardiac index (l/min/m²)</th>
<th>Mean PCW (mm Hg)</th>
<th>Duration of dyspnea (mo)</th>
<th>Age (yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17.6 ± 3.0</td>
<td>33.7 ± 8.8</td>
<td>3.6 ± 3.3</td>
<td>4.0 ± 3.3</td>
<td>34.0 ± 2.8</td>
<td>0.34 ± 0.04</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>17.2 ± 3.7</td>
<td>32.4 ± 6.5</td>
<td>8.5 ± 12.1</td>
<td>10.6 ± 7.2</td>
<td>29.4 ± 5.0</td>
<td>0.40 ± 0.11</td>
<td>33 ± 14</td>
<td>—</td>
<td>—</td>
<td>3 ± 3</td>
<td>53 ± 11</td>
</tr>
<tr>
<td>3</td>
<td>17.6 ± 3.3</td>
<td>30.5 ± 7.2</td>
<td>3.6 ± 0.9</td>
<td>6.4 ± 4.2</td>
<td>39.2 ± 11.0</td>
<td>0.37 ± 0.06</td>
<td>72 ± 13</td>
<td>4.0 ± 0.9</td>
<td>8.8 ± 1.9</td>
<td>0</td>
<td>49 ± 8</td>
</tr>
<tr>
<td>4</td>
<td>23.9 ± 1.0</td>
<td>46.4 ± 4.3</td>
<td>1.3 ± 0.6</td>
<td>10.7 ± 5.9</td>
<td>29.0 ± 3.2</td>
<td>0.50 ± 0.06</td>
<td>44 ± 20</td>
<td>2.7 ± 0.8</td>
<td>11.5 ± 12.0</td>
<td>16 ± 13</td>
<td>40 ± 18</td>
</tr>
<tr>
<td>5</td>
<td>18.7 ± 3.4</td>
<td>47.6 ± 12.1</td>
<td>7.8 ± 1.9</td>
<td>16.6 ± 6.4</td>
<td>29.3 ± 15.0</td>
<td>0.51 ± 0.25</td>
<td>40 ± 13</td>
<td>2.3 ± 0.9</td>
<td>8.7 ± 7.2</td>
<td>21 ± 33</td>
<td>47 ± 17</td>
</tr>
<tr>
<td>6</td>
<td>22.7 ± 2.7</td>
<td>48.2 ± 8.0</td>
<td>2.5 ± 2.0</td>
<td>24.9 ± 14.4</td>
<td>20.5 ± 5.0</td>
<td>0.58 ± 0.04</td>
<td>25 ± 3</td>
<td>3.1 ± 0.2</td>
<td>32 ± 6</td>
<td>37 ± 41</td>
<td>30 ± 10</td>
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<tr>
<td>7</td>
<td>23.0 ± 5.1</td>
<td>41.3 ± 9.6</td>
<td>5.6 ± 2.0</td>
<td>12.5 ± 4.5</td>
<td>19.3 ± 12.6</td>
<td>0.45 ± 0.13</td>
<td>27 ± 15</td>
<td>2.3 ± 0.8</td>
<td>25.2 ± 7.3</td>
<td>28 ± 32</td>
<td>55 ± 13</td>
</tr>
<tr>
<td>8</td>
<td>23.3 ± 5.1</td>
<td>47.2 ± 8.1</td>
<td>8.0 ± 7.2</td>
<td>10.1 ± 9.3</td>
<td>15.9 ± 4.0</td>
<td>0.61 ± 0.09</td>
<td>23 ± 9</td>
<td>2.2 ± 0.7</td>
<td>25.7 ± 8.3</td>
<td>23 ± 20</td>
<td>48 ± 12</td>
</tr>
<tr>
<td>9</td>
<td>20.3 ± 3.9</td>
<td>40.9 ± 9.6</td>
<td>1.9 ± 1.1</td>
<td>12.2 ± 6.6</td>
<td>23.0 ± 13.0</td>
<td>0.59 ± 0.12</td>
<td>37 ± 23</td>
<td>3.1 ± 0.7</td>
<td>15.5 ± 9.0</td>
<td>4 ± 2</td>
<td>37 ± 10</td>
</tr>
<tr>
<td>10</td>
<td>20.4 ± 3.9</td>
<td>37.9 ± 10.2</td>
<td>5.7 ± 9.6</td>
<td>9.6 ± 7.6</td>
<td>18.3 ± 7.5</td>
<td>0.57 ± 0.13</td>
<td>31 ± 17</td>
<td>2.5 ± 0.9</td>
<td>18.5 ± 8.2</td>
<td>18 ± 36</td>
<td>49 ± 15</td>
</tr>
</tbody>
</table>

Combined groups (total) | 20.0 ± 4.4 | 38.2 ± 10.1 | 5.8 ± 8.0 | 9.8 ± 7.3 | 23.4 ± 10.2 | 0.49 ± 0.15 | 33 ± 19 | 2.6 ± 0.9 | 19.3 ± 9.3 | 19 ± 9 | 49 ± 14 |

Each value is mean ± SD; p statistic represents a significant difference from normal group value.

PEP/LVET = the ratio of the prejection period to left ventricular ejection time of the systolic time intervals; mean PCW = mean pulmonary capillary wedge pressure.

**Results.**

The average histologic, hemodynamic, and clinical characteristics of patients in each group are shown in table 1. Statistical analysis was applied to several histologic, hemodynamic, and clinical data from all of the patients to determine significant trends (table 2). The histologic characteristics correlated with each other, the strongest correlation being between cell diameter and nuclear area (r = .70, p < .001). The percentage of fibrosis showed a weak correlation with cell diameter (r = .30, p < .005) and with nuclear area (r = .29, p < .005). Results of several of the function studies correlated, albeit weakly, with histologic factors; the strongest correlations were those between echocardiographic %ΔD and cell diameter (r = –.33, p < .005) and %ΔD and nuclear area (r = –.35, p < .005). The clinical characteristics of duration of dyspnea and age of the patient did not correlate with any of the histologic or hemodynamic study results.

Intragroup data analyses were also performed and the correlations obtained were generally similar to those obtained when all 109 patients were considered together. However, the correlations for the four largest groups were better when considered individually. The
TABLE 2
Correlations between histologic, hemodynamic, and historical features

<table>
<thead>
<tr>
<th></th>
<th>Cell diameter (µm)</th>
<th>Nuclear area (µm²)</th>
<th>Endocardial thickness (µm)</th>
<th>% Fibrosis</th>
<th>%ΔD</th>
<th>Ejection fraction (%)</th>
<th>Cardiac index (l/min/m²)</th>
<th>PCW (mm Hg)</th>
<th>Duration dyspnea (mo)</th>
<th>Age (yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nuclear area (µm²)</td>
<td>.70(109)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.08(109)</td>
</tr>
<tr>
<td>Endocardial thickness (µm)</td>
<td>-.04(109)</td>
<td>-.03(109)</td>
<td></td>
<td>.30(109)</td>
<td></td>
<td>.15(109)</td>
<td>-.13(70)</td>
<td></td>
<td>.17(98)</td>
<td>.02(109)</td>
</tr>
<tr>
<td>% Fibrosis</td>
<td></td>
<td>.29(109)</td>
<td>.16(91)</td>
<td>.52(59)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.12(98)</td>
<td>.14(109)</td>
</tr>
<tr>
<td>%ΔD</td>
<td>-.33(81)</td>
<td>-.02(80)</td>
<td>-.20(80)</td>
<td>-.07(98)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.03(83)</td>
<td>.01(109)</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>.23(92)</td>
<td>.16(91)</td>
<td>.15(91)</td>
<td>.14(91)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.06(109)</td>
</tr>
<tr>
<td>PCW (mm Hg)</td>
<td>.32(67)</td>
<td>.25(67)</td>
<td>.12(67)</td>
<td>.14(67)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.02(109)</td>
</tr>
<tr>
<td>Duration dyspnea (mo)</td>
<td>.17(98)</td>
<td>-.03(97)</td>
<td>-.07(97)</td>
<td>.03(83)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.06(109)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.01(109)</td>
</tr>
</tbody>
</table>

This table presents the r value, the number of observations (in parentheses), and the p statistic for each significant correlation. Abbreviations are as in table 1.

correlations between cell diameter and percentage of fibrosis and cell diameter and echocardiographic %ΔD are shown in figures 1 and 2. In addition, there was a correlation between cell diameter and age (r = .67, p < .05; figure 3) in group 1 (10 normal subjects).

Patients with idiopathic CHF were divided into two groups: those with hypertension and those who were normotensive. Cell diameter was significantly greater in the hypertensive patients (22.2 ± 3.8 vs 19.6 ± 3.8 µm, p < .05). Percentages of fibrosis were not different in these two subpopulations. In the idiopathic CHF group as a whole there were good correlations between cell diameter and nuclear area (r = .67, p < .0001) and cell diameter and fibrosis (r = .54, p < .001).

Because cardiac function in the various groups was not equal, the comparison of the histologic characteristics among the four major groups was accomplished by
comparing the slopes for the individual groups. These slopes were inscribed by plotting the cell diameter (figure 2) or percentage of fibrosis (figure 3) against the echocardiographic %ΔD. The linear regression analyses were forced through a "normal" point derived from the data of the 10 normal subjects in this study. This was done because we assumed that each patient was normal before myocardial insult. Thus, the line for each group should reflect the pathway of the myocardial response to injury.

The comparison of slopes for the change in cell size with progressive heart failure (as determined by the echocardiographic %ΔD) is shown in figure 2 for the four largest groups. The slope inscribed by the data from the alcohol-induced CHF group was significantly different from that inscribed by data from doxorubicin-treated patients (p < .05). The idiopathic and valvular CHF group slopes were intermediate and not significantly different from those for either the alcohol-induced CHF or doxorubicin-treated groups. Figure 3 illustrates the slopes derived for fibrosis plotted against %ΔD. The doxorubicin-treated group was significantly different from the alcohol-induced and idiopathic CHF groups (both p < .05), but not from the valvular CHF group. The valvular CHF group did not differ from any of the others.

Discussion

Methodologic considerations. The use of quantitative histologic procedures in endomyocardial biopsies is plagued by the problems of sampling error and fixation artifact. The biopsied tissue used in this study was all taken from the right side of the interventricular septum. However, Baandrup and Olsen2 have shown that right ventricular endomyocardial biopsy samples are equivalent to those removed from the left. In addition, our laboratory demonstrated a consistent pattern of fibrosis, vacuolization, and hypertrophy in samples from the right and left.18 Although there are varying degrees of degeneration at different levels of the myocardium, the patterns are consistent in CHF.18 Also, in a study of myocardial biopsy samples taken close to the time of death, it was demonstrated that these samples were representative of overall cardiac pathology.3,19 Thus, right-sided endomyocardial biopsies can be used to determine cardiac morphologic alterations and can be compared with biopsies of the same area of the hearts of normal subjects and other CHF patients.

Fixation artifact is primarily a problem in electron microscopy but can cause some vacuolization in light-microscopic specimens.20 This problem has been obviated by the use of tissue samples of similar size (1 to 2 mm²), eliminating cells with contraction-band artifacts, and the use of the same techniques for the processing of all tissues.

Histologic and clinical correlations. For the total patient population (n = 109), in which there was a spectrum of normal-to-severe CHF and disparate causes of disease, several interesting correlations were noted. As expected, cell diameter correlated closely with nuclear area (r = .70, p < .0001). Increased nuclear activity (and therefore size) is a primary requisite for cellular hypertrophy.21,22 There were also weak correlations between percentage of fibrosis and cell diameter (r = .30, p < .005) and percentage of fibrosis and nuclear area (r = .29, p < .005). This was also expected because hypertrophy is a stimulus for fibrosis.23,24 The low r value (.30) probably reflects the many factors besides hypertrophy that promote fibrosis. Endocardial thickness was independent of the other histologic markers.

Cell diameter correlated weakly with cardiac function measures such as echocardiographic %ΔD (r = −.33, p < .005), the ratio of prejection period/left ventricular ejection time (r = .23, p < .05), and mean pulmonary capillary wedge pressure (r = .32, p < .01). The correlation between cell diameter with echocardiographic %ΔD improved, however, when individual groups were considered independently and when the regression lines were forced through a normal point (figure 1). This suggests an association of worsening heart function with increasing cellular hypertrophy.

Amount of fibrosis also correlated poorly with measures of myocardial function for the total population, but improved for individual groups (figure 2). Percentage of fibrosis did not correlate with mean pulmonary
capillary wedge pressure. These results are consistent with those of a previous study\textsuperscript{25} that showed that fibrosis was less important than cellular hypertrophy or myocardial adenosine triphosphate content in raising left ventricular filling pressure. Endocardial thickness did correlate weakly with ejection fraction ($r = .24$, $p < .05$) and cardiac index ($r = .25$, $p < .005$).

None of the histologic measurements correlated with the duration of dyspnea or the patient age. Baandrup et al.\textsuperscript{6} also did not find a relationship between the duration of disease and histologic change. Shirey et al.\textsuperscript{26} however, did find that amounts of fibrosis and cellular hypertrophy correlated with prognosis. We did not address the question of prognosis.

**Myocardial response to insult.** One purpose of this study was to determine whether different myocardial insults resulted in certain pathologic responses. An important negative finding of this study was that, in this regard, no difference could be detected between the valvular, idiopathic, and alcohol-induced CHF groups. The doxorubicin-treated group was distinguishable, however. For a given loss of systolic myocardial function (as measured by the echocardiographic %ΔD), the alcohol-induced CHF group had the greatest hypertrophy, while the doxorubicin-treated group had the least (figure 1). Doxorubicin, an effective cancer chemotherapeutic drug, intercalates DNA\textsuperscript{27, 28} and interferes with protein production.\textsuperscript{29, 30} Human myocardial nuclear studies have demonstrated signs of doxorubicin-induced nuclear degeneration.\textsuperscript{31} We hypothesize that the nuclear effect of doxorubicin inhibits myocardial cell growth. The mechanism for the markedly increased hypertrophy induced by alcohol is not clear.

Percentage of fibrosis in myocardium of patients also showed that doxorubicin injury was distinct from the other types (figure 2). Fibrosis was most severe in doxorubicin-treated patients and least severe in those with idiopathic CHF and alcohol-induced injuries ($p < .05$).

Within the individual groups interesting relationships were observed that facilitate understanding of the myocardial response to injury. The normal group was quite interesting because of the good correlation ($r = .67$) between age and cell size (figure 3), but not between age and percentage of fibrosis. Aging may be an insult to the human myocardium that results in hypertrophy but not fibrosis and the previously described alterations in contractile properties in the aging heart\textsuperscript{32} may be related to cellular hypertrophy. Only 10 patients were included in our normal group and further studies are needed to corroborate this data.

Group 2, which included those with doxorubicin-induced cardiomyopathy, was unique because there was little to no hypertrophy observed, but amount of fibrosis was markedly increased, as previously discussed. Amount of fibrosis did not correlate with the total cumulative dose of doxorubicin, suggesting a widely disparate fibrotic reaction of the individual patients’ hearts. This is consistent with the clinical experience, which shows that some patients are less tolerant of doxorubicin because they are older,\textsuperscript{33, 34} had previous radiation therapy,\textsuperscript{35} or underwent other cardiotoxic chemotherapy,\textsuperscript{36, 37} while some patients can tolerate massive doses.

Group 3 patients, who had chest pain with normal coronary arteries, did not differ from the normal group in any of the histologic or hemodynamic characteristics. Groups 4 through 6 (familial, myotonic dystrophy, and peripartum CHF) were small so that they could not be effectively distinguished from patients with other types of CHF. However, the familial CHF patients ($n = 3$) had the largest cells and as a group had only modest heart failure. The peripartum CHF patients ($n = 2$) had the most pronounced fibrosis and only moderate heart failure.

Valvular heart disease patients demonstrated an average amount of fibrosis and cellular hypertrophy commensurate with the degree of myocardial dysfunction (figures 1 and 2). Alcohol-induced CHF patients, in addition to having remarkable hypertrophy, were the only patients in which a correlation between amount of fibrosis and endocardial thickness could be demonstrated ($r = .56$, $p < .05$). This relationship had been expected to hold for the total patient population but it did not.

The idiopathic CHF group probably contained several ill-defined subgroups. Hypertension seemed to distinguish one subgroup with more cellular hypertrophy. Many of the patients in group 10 were probably victims of a subclinical viral myocarditis. However, the light-microscopic characteristics of the postviral and the idiopathic CHF groups were not similar. Further analysis and definition of this group will be necessary to understand the pathogenesis of cellular injury.

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**References**

2. Baandrup U, Olsen EJ: Critical analysis of endomyocardial biop-
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D V Unverferth, J K Fetters, B J Unverferth, C V Leier, R D Magorien, A R Arn and P B Baker

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