

## Insensitivity of Right Ventricular Endomyocardial Biopsy in the Diagnosis of Myocarditis

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The clinical suspicion of myocarditis relies strongly on endomyocardial biopsy for confirmation, yet the sensitivity of the procedure in this setting has not been clearly defined. Biopsy sensitivity was determined in 14 hearts with histologically proved myocarditis studied *ex vivo*, including 12 autopsy hearts and 2 native hearts explanted at cardiac transplantation. With use of the Stanford and Cordis biotomes, endomyocardial biopsy was performed near the apex on the right side of the ventricular septum (four to five samples/biotome per patient) and repeated in the nonapical portion of the septum from the moderator band to the subpulmonary infundibulum (additional three to five samples/biotome per patient).

In a casewise assessment, 43% to 57% of the endomyocardial samples were diagnostic for myocarditis, as calculated separately for each biotome in each region of sam-

pling (apical/nonapical). Both apical and nonapical sensitivity improved to 64% when the findings of the two biotomes were combined (eight to nine samples/patient in each region). By collectively analyzing all available samples for each patient, 11 (79%) of 14 cases could be diagnosed, but this required a mean of 17.2 samples/patient, a number clinically unrealistic. The exclusion of four cases of fungal myocarditis from analysis did not significantly alter the results. In transmural ventricular sections, none of four patients with sudden death had inflammatory disease confined to the conduction system.

In conclusion, despite six to eight negative biopsy samples/patient with suspected myocarditis, repeat biopsy may still be warranted.

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The transvenous endomyocardial biopsy is essential to the current diagnostic evaluation of myocarditis. However, early concerns regarding the utility of the biopsy in cardiomyopathy and other forms of heart disease (1) recurred a decade later in the context of unexplained heart failure and myocarditis (2). Despite quantitative (3) and qualitative (4) criteria and the illustrated use of endomyocardial biopsies in myocarditis (5,6), challenges remain in understanding the role of lymphocytes in cardiomyopathic disease (7) and in the evaluation of mononuclear cells in heart tissue (8,9). The degree of interobserver variability (10) has been addressed by the widely accepted histopathologic working criteria for myocarditis (4). The issue of natural variability of myo-

carditic infiltrates and the potential for biopsy sampling error have not been resolved.

The residual uncertainty of a negative biopsy finding was tested by Spiegelhalter and Stovin (11) in cardiac allograft rejection. By constructing a statistical model, these investigators determined that three negative specimens would be sufficient if a 5% chance of a mild rejection was acceptable evidence not to alter therapy, whereas four negative samples would reduce the error rate to 2%. By plotting the incremental improvement in the sensitivity for moderate rejection in autopsy-acquired samples, Zerbe and Arena (12) demonstrated a plateau in the sensitivity at values of 90% to 93% when six or more samples were obtained. Baandrup et al. (13) found a minimum of five biopsy specimens necessary to reliably establish the structural relations on the cellular diameters and the volume fractions of collagen and the interstitium in the heart. More recently, the preliminary data of Hauck et al. (14) showed that despite 10 biopsy samples/ventricle in each of 38 cases of lymphocytic myocarditis, the frequency of false negative results was 37% for the right ventricle and 45% for the left ventricle.

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**Table 1.** Right Ventricular Endomyocardial Biopsy in 14 Cases of Myocarditis

Histologic Category	Age (yr) & Gender	Clinical Presentation	No. of Samples*				Severity of Myocarditis†	
			SA	CA	SN	CN	Autopsy‡	17.2 Emb/Pt§
<b>Mixed mononuclear cell</b>								
Case 1	50/F	Heart failure	5	5	5	4	++	±
Case 2	52/M	Sudden death	5	5 (2)	5 (1)	4	++	++
Case 3	70/F	Heart failure	5	5	5	4	++	0
Case 4	21/F	Sudden death	5	3 (1)	5	5 (2)	+	+
Case 5	46/M	Heart failure	5 (1)	2 (2)	4 (3)	3 (1)	+	+
Case 6	4/M	Shock	5 (3)	4 (3)	5 (2)	4 (2)	+	+
<b>Granulomatous</b>								
Case 7	40/F	Sudden death	5	4	5 (1)	5	+++	+
Case 8	1/F	Sudden death	3 (3)	0	4 (4)	0	++	++
<b>Giant cell</b>								
Case 9	54/M	Heart failure	5 (5)	4 (4)	5 (5)	5 (5)	+++	+++
<b>Rheumatic</b>								
Case 10	52/M	Heart failure	5 (2)	3	5	3	+	+
<b>Fungal</b>								
Case 11	36/M	Septicemia	5	4	4	5	++	0
Case 12	41/F	Septicemia	5	4	5 (1)	4 (1)	++	+
Case 13	69/M	Granulocytopenia	5 (1)	3	5 (1)	5 (2)	++	+
Case 14	36/F	Septicemia	5	4 (2)	5	5	+	+

\*Biopsy samples were obtained at apical and nonapical septal sites using two bioptomes (CA = Cordis bioptome, apical; CN = Cordis bioptome, nonapical; SA = Stanford bioptome, apical; SN = Stanford bioptome, nonapical). The number of positive samples is indicated in parentheses. †Myocarditis: 0 = none; ± = borderline; + = mild; ++ = moderate; +++ = severe. ‡The heart in Cases 5 and 10 was a native organ explanted at cardiac transplantation. §Based on at least one positive sample/patient (Emb/Pt), with 17.2 samples/patient (mean). F = female; M = male.

The processes of allograft rejection, myocarditis, fibrosis and hypertrophy are distinct enough in nature and extent that their respective evaluation by endomyocardial biopsy may be differentially successful. To further define biopsy sensitivity in myocarditis, we sampled the right side of the ventricular septum in 14 patients with histologically proved myocarditis, accommodating for differences in the size and location of the samples.

## Methods

**Study patients (Table 1).** Fourteen patients with myocarditis were studied (seven male and seven female, ranging in age from 1 to 70 years [mean 40.9]). Twelve of the patients died, and two others required cardiac transplantation for treatment. Six patients presented initially with heart failure or shock, four with sudden death and four with systemic fungal infection complicating other medical conditions. The heart was studied *ex vivo*, either at autopsy or during orthotopic allograft placement. Histologic evaluation of multiple transmural slices of the ventricular myocardium revealed mixed mononuclear cell (n = 6), granulomatous (n = 2), giant cell (n = 1), rheumatic (n = 1) and fungal (n = 4) myocarditis in these patients.

**Catheter bioptomes.** Two adult bioptomes were used: the Stanford bioptome (9F, Scholten Surgical Instruments) and

the Cordis disposable bioptome (5.4F, catalog no. 502-302). Both devices are clinically employed in the cardiac catheterization laboratory for transvenous endomyocardial biopsy by the internal jugular approach. The Cordis bioptome (1.84 mm<sup>3</sup> sample volume) provides tissue fragments approximately one-third the volume of those provided by the Stanford bioptome. This difference permitted an evaluation of the influence of sample size on diagnosis.

**Sampling strategy.** Apical endomyocardial samples were obtained from the right side of the ventricular septum. Each bioptome was advanced across the tricuspid valve from the direction of the superior vena cava, and sample location was verified by inspection. The right ventricular cavity was then opened, and paired specimens were taken by the adjacent placement of each bioptome in the nonapical septum at multiple locations evenly distributed from the moderator band to the subpulmonary infundibulum.

**Evaluation of myocarditis.** After staining with hematoxylin-eosin (12 stepped levels) and with Masson's trichrome (4 levels), each biopsy sample was histologically evaluated for myocarditis according to the Dallas criteria (4). The severity of disease and the character of the cellular infiltrate, if present, were documented. For comparison, full-thickness ventricular slices from all patients were sectioned, stained and similarly examined for the maximal severity of disease and the character of the cellular infiltrate.

**Observer variability.** Each endomyocardial sample was interpreted on two separate occasions by a certified pathologist (B.M.M.) familiar with the Dallas criteria (4) and unaware of all clinical data and autopsy or explant findings, yielding an intraobserver correlation coefficient of 0.86 (Spearman rank correlation). Independent assessment on a separate occasion by a second certified cardiovascular pathologist (S.J.R.) yielded correlation coefficients of 0.80 and 0.78, respectively, compared with the readings of the first examiner.

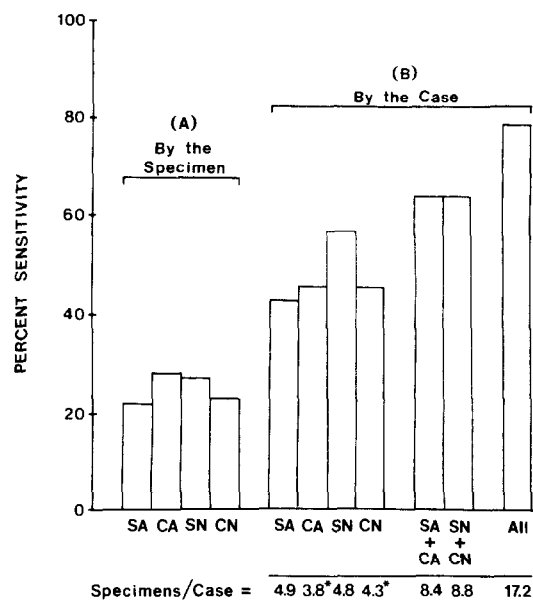
**Biopsy sensitivity.** Positive biopsy samples were those showing definite myocarditis; samples with borderline myocarditis were considered separately, as designated in the Results section. Diagnostic sensitivity "by the specimen" expressed the likelihood of a positive diagnosis in an individual biopsy sample; sensitivity "by the case" reflected the frequency of at least one positive sample in a patient, analogous to the typical evaluation of multiple samples from a single patient. In casewise analysis, the sensitivity was considered first for each bioptome in each region of sampling (apical/nonapical), then for the results pooled between the bioptomes in the respective regions and lastly by combining all the available samples in each patient.

### Results

**Endomyocardial samples.** The number of biopsy samples available in each case is listed in Table 1. On average ( $\pm$  SD),  $4.9 \pm 0.5$  and  $4.8 \pm 0.4$  samples/patient were obtained with the Stanford bioptome from the apical and nonapical septum, respectively. With the Cordis bioptome, the corresponding figures were  $3.8 \pm 0.9$  and  $4.3 \pm 0.8$  samples/patient, respectively, excluding one infant in whom no sample was available with this bioptome. In total, there were  $17.2 \pm 3.3$  biopsy specimens for each patient.

**Diagnostic sensitivity (Fig. 1).** On the basis of the frequency of positive biopsy samples in Table 1, the diagnostic sensitivity was calculated for each bioptome in each region of sampling. For individual biopsy samples, the sensitivity ranged from 22.1% to 28.0%, without a significant difference between the apical and the nonapical samples or between the Stanford and the Cordis bioptomes ( $p = 0.90$  by chi-square analysis, 3 degrees of freedom, raw frequency data). Fifty-five specific comparisons of nonapical samples obtained with the two bioptomes from immediately adjacent sites gave an identical sensitivity of 23.6% for each bioptome. Notably, however, only 10 of the 13 diagnostic samples from one bioptome had a paired sample that was also positive by the other bioptome.

On the basis of multiple samples from each patient, the casewise analysis of sensitivity was performed to more accurately reflect clinical practice, such that a minimum of one clearly abnormal sample would be sufficient for diagnosis (Fig. 1). The casewise sensitivity ranged from 42.9% to



**Figure 1.** Diagnostic sensitivity of right ventricular endomyocardial biopsy. The sensitivity of a single biopsy specimen (A) and the sensitivity of samples assessed by the case (B) are shown. The latter represents the frequency of at least one positive sample in each patient. Data are separated by the region of sampling and the bioptome used. \*Excludes one infant case for which no sample was available with this bioptome (Cordis). CA = Cordis bioptome, apical; CN = Cordis bioptome, nonapical; SA = Stanford bioptome, apical; SN = Stanford bioptome, nonapical.

57.1%. without a significant difference between the two bioptomes or between apical and nonapical sites of sampling ( $p = 0.95$  by chi-square analysis, 3 degrees of freedom, raw frequency data). In the apical septum, where samples from the two bioptomes were not paired, each bioptome yielded diagnostic findings for myocarditis in six cases, with both bioptomes giving positive results in three of these cases.

In the absence of a significant difference between the sampling sensitivity of the two bioptomes, the endomyocardial samples were pooled to give an average of 8.4 and 8.8 specimens/patient in the apical and nonapical septum, respectively. In this way, the casewise sensitivity reached 64.3% for the apical and the nonapical samples alike (Fig. 1). Furthermore, because there was no significant difference in the diagnostic sensitivity between the apical and the nonapical samples, all available specimens in each patient were analyzed collectively. With this procedure, myocarditis could be diagnosed in 11 of the 14 cases, which is equal to a sensitivity of 78.6%, but at a mean ( $\pm$  SD) requirement of  $17.2 \pm 3.3$  samples/patient, which is clearly unattainable in clinical practice.

**Borderline myocarditis.** By the Dallas criteria (4), a biopsy sample showing equivocal histologic findings for myocarditis is termed borderline and may indicate the need for

repeat biopsy in patients in whom a strong clinical suspicion of myocarditis remains. When samples histologically borderline for myocarditis were included for calculation in this study, the sensitivity of an individual sample increased to 33.2%, whereas the casewise sensitivity improved to 62.8% in the absence of pooling between biotomes or septal regions and to 85.7% with all the samples pooled in each patient.

**Fungal myocarditis.** Although fungal infections secondarily involving the myocardium would not normally rely on endomyocardial biopsy for evaluation, analysis of our data after excluding cases of fungal myocarditis produced virtually no change in results, with increased biopsy sensitivity limited to 1% to 6% at each level of comparison (by the specimen or by the case, with or without pooling between biotomes or locations of sampling).

**Sudden death.** Myocarditis manifested as sudden death may represent a subset of the disease that differs histologically from myocarditis causing heart failure. The spectrum of severity of myocarditis by full autopsy or explant examination was similar in cases of heart failure and sudden death in this study (Table 1), and biopsy sensitivity assessed for each biotome in each region of sampling and for each level of pooling showed no statistically significant difference in patients with sudden death versus those with heart failure ( $p = 0.20$  by Mann-Whitney U test). Moreover, transmural sections of the ventricular septum, obtained specifically at sites sampled by biopsy, confirmed the presence of myocarditis in the vicinity of biopsy in all four patients with sudden death, and excluded disease isolated to the conduction system in these patients.

**Severity of myocarditis.** The maximal severity of disease is shown in Table 1 for all patients. On the basis of histologic assessment of random transmural ventricular sections, two patients had severe, seven had moderate and five had mild myocarditis. In contrast, the grade of myocarditis observed in the biopsy samples was generally less, with eight patients judged to have mild disease. One of the latter (Patient 7) presented with sudden death and had severe granulomatous myocarditis in transmural sections (Fig. 2A and B); 18 of the 19 biopsy specimens in this patient were negative for myocarditis, and the single sample judged mildly positive is shown in Figure 2C and D. Three patients without myocarditis by biopsy had moderate disease on full histologic examination.

**Infiltrate morphology.** The infiltrating cell types were poorly represented in the endomyocardial biopsy samples. Among the cases positive for myocarditis by biopsy, one granulomatous, one rheumatic and two fungal cases could not be subclassified accordingly. The histologic impression on biopsy was generally one of mixed mononuclear cell infiltration.

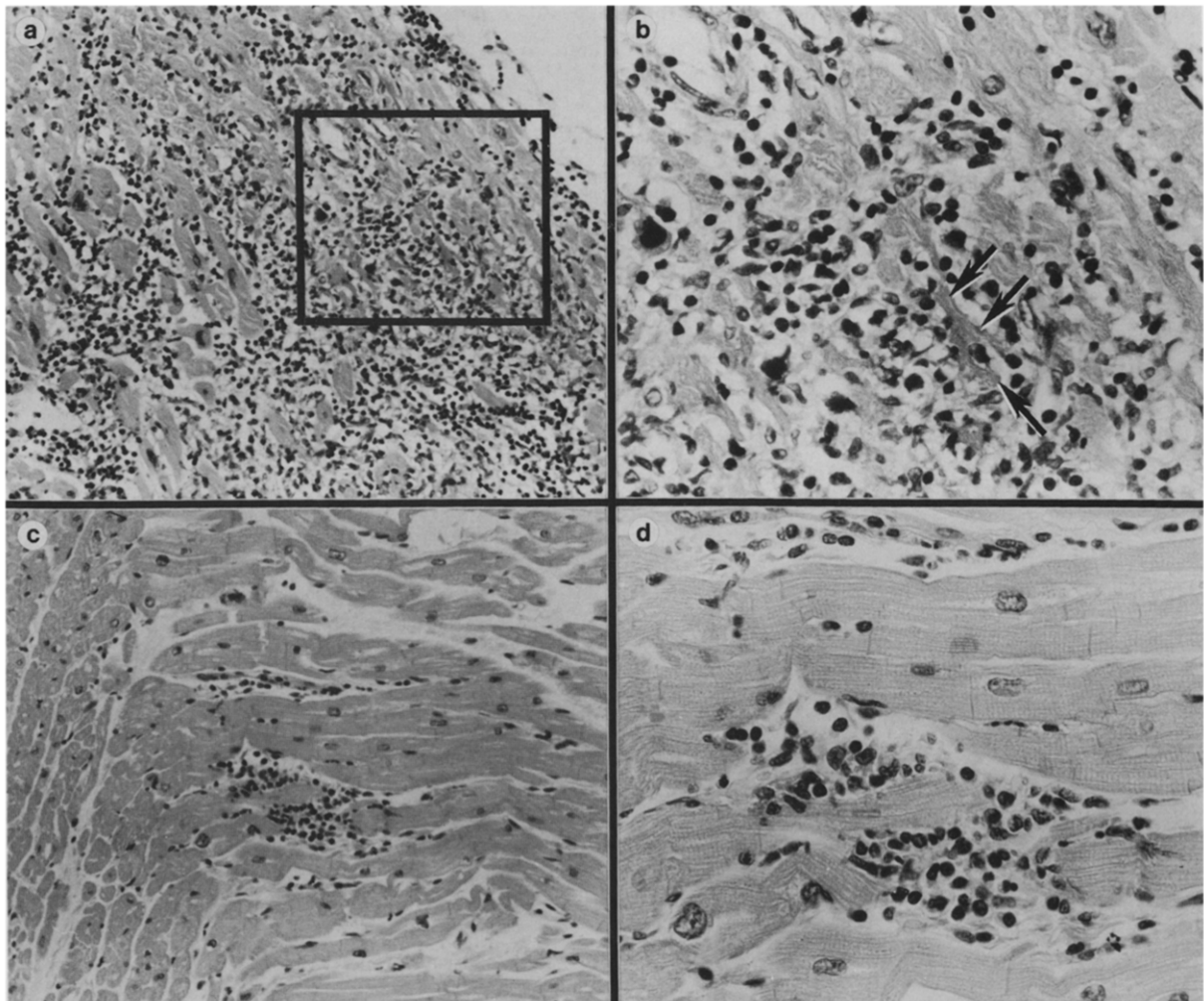
## Discussion

**Limited biopsy sensitivity.** Biopsy sampling of the right ventricular endomyocardium from the ventricular septum of 14 patients with histologically confirmed myocarditis demonstrated relatively low levels of diagnostic sensitivity. With four to five samples/patient, the chance of a successful diagnosis was near 50%. Although 11 of 14 cases could be diagnosed after the cumulative pooling of samples, an average of >17 samples/case was required. The statistical evaluation by Spiegelhalter and Stovin (11) gave a considerably more optimistic outlook in the setting of cardiac allograft rejection; the latter has been substantiated by the empirical data of others (12,15) and by our own experience in a separate study of biopsy sampling in failed human heart allografts (unpublished data).

In a recent abstract, Hauck et al. (14) presented their findings of endomyocardial sampling with the Cordis biotome in 38 autopsy hearts with lymphocytic myocarditis. They found myocarditis in only 66 (17%) of 380 biopsy samples from the right ventricle and 76 (20%) of 380 samples from the left ventricle. Furthermore, with 10 biopsy samples/ventricle per patient, their casewise sensitivity was 63% for the right ventricle and 55% for the left. Thus, there is a concordance of contemporary but fully independent observations from their laboratory and ours, which strongly emphasizes the significance of the results.

**Histologic subsets.** Besides purely lymphocytic myocarditis, eosinophilic, giant cell and other forms of inflammatory infiltrates are included within the working (Dallas) criteria for the diagnosis of myocarditis (4). Although at times granulomatous and giant cell myocarditis are a manifestation of known systemic conditions, they are frequently idiopathic. Moreover, the clinician presented with suspected myocarditis cannot justifiably discriminate among histologic subsets. Rheumatic myocarditis without significant valvular involvement may be first recognized only after histologic examination after cardiac allograft replacement (unpublished observations). Accordingly, in the present study we endeavored to include myocarditis of different origins. In this respect, cases of fungal myocarditis, although not ordinarily assessed by endomyocardial biopsy, did not influence the overall results when they were excluded from analysis. These observations suggest that there is an inherent limitation of current biotome approaches that is more important in determining biopsy sensitivity than the uniqueness of a given histologic subset of myocarditis.

**Sudden death.** Patients with sudden death may present for endomyocardial biopsy when successfully resuscitated (16). That the heart in patients with sudden death in our study clearly had disease present within the "working" ventricular septal myocardium suggests that isolated fortuitous involvement of the conduction system does not characterize such patients and may not account for their death.



**Sample volume.** From our study, it appeared that the focal nature of the myocarditic lesions negated any advantage of a larger sample obtainable with the Stanford biop-  
tome because the Stanford and the Cordis biop-  
tomes showed virtually identical sensitivity. Nevertheless, the results with the two biop-  
tomes differed significantly in individual cases, a finding that served only to illustrate the unpre-  
dictable distribution of the myocarditic lesions.

**Sample location.** Altering the site of endomyocardial sampling away from the customary location in the right ventricular apical septum did not improve diagnostic sensi-  
tivity. The nonapical septal samples in our study and the left ventricular samples in the study by Hauck et al. (14) did not produce superior results.

**Newer histologic methods.** The use of immunohisto-  
chemic markers for lymphocytes and other infiltrating cell types in transmural myocardial specimens has improved the detection and quantitation of these cells (8,9). What role such techniques have in the evaluation of biopsy samples in myocarditis requires more study. Immunoperoxidase staining for leukocyte common antigen in 199 consecutive endo-

**Figure 2.** Patient 7. Histologic assessment of transmurular ventricular section versus endomyocardial biopsy sample. This 40 year old woman died suddenly and was found to have severe granulomatous myocarditis in transmural ventricular sections obtained at postmor-  
tem examination (a). The subendocardial area outlined in a is shown under higher power in b, demonstrating an admixture of typical lymphocytes, histiocytoid forms and possible giant cells and an appearance of interstitial edema. An irreversibly damaged, hyper-  
eosinophilic and partially vacuolated cardiomyocyte is indicated by the arrows. From a total of 19 endomyocardial biopsy samples obtained ex vivo in this patient, only 1 sample was judged positive on the basis of a single focus of mild disease shown entirely in c and under higher power in d. Hematoxylin-eosin stain; original magnification  $\times 125$  in a and c and  $\times 330$  and b and d.

myocardial biopsy samples of various diagnostic categories (17) showed that the leukocyte count in myocarditis, despite having a significantly higher mean value, overlapped considerably with those of the other patient groups. Nonetheless, a role for this technique in borderline cases of myocarditis was advocated as a complement to conventional staining. More specific monoclonal reagents to whole populations or sub-

sets of lymphocytes or to muscle-specific actin, including many additional markers effective in formalin-fixed, paraffin-embedded tissues in myocarditis (18), remain to be tested in endomyocardial biopsy samples.

A prospective study (19) of 79 patients with myocarditis or dilated cardiomyopathy demonstrated a strong association between immunofluorescent staining for immunoglobulin and complement deposits and the presence of inflammatory infiltration in endomyocardial biopsy material. A gain in diagnostic sensitivity, however, cannot be expected without a revision of the current criteria to include immunofluorescence data. In the same study, electron microscopy of the biopsy samples gave valuable prognostic information, but did not predict myocarditis.

**Prospectus.** Despite apparently limited sensitivity, the endomyocardial biopsy has essential value in cases of suspected myocarditis because diagnostic confirmation is otherwise difficult. In this regard, the Dallas Criteria (4) remain the working standard for the histopathologic diagnosis of myocarditis, and these criteria applied by a pathology panel (of which B.M.M. is a member) form the foundation of patient entry into an ongoing National Institutes of Health-sponsored multicenter Myocarditis Treatment Trial. The objectivity of pathologists interpreting endomyocardial biopsy specimens is unaffected by the caveat of biopsy sensitivity discussed in this report. As well, detection of myocarditis may be achieved by timely biopsy in many living patients suspected of having myocarditis with the number of tissue samples currently obtained in the clinical setting. We do believe that an important challenge lies in improving current diagnostic methods through novel means of sampling or further refinements in the approach to histologic assessment. On the basis of our findings and those of others (14), we recommend that repeat biopsy be considered in patients strongly suspected to have myocarditis in order to increase the number of tissue samples available for histologic analysis.

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