Clinical Merit of Endomyocardial Biopsy

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There was hope that endomyocardial biopsy would provide pathogenic information leading to subclassification and specific treatment of idiopathic dilated cardiomyopathy. This is an objective that has not been met. Achievement of this goal will clearly require the pathologist to move beyond the standard tools of light and electron microscopy to new and emerging techniques that go beyond visual interpretation of tissue and cellular morphology. The once-novel act of safely obtaining human myocardial biopsy specimens nonsurgically, then within the purview of only a few experts, is now trifling. It is what is done with the tissue that counts now.

Widespread Use

It is a paradox that as scientific evidence for lack of therapeutic usefulness of cardiac biopsy in idiopathic dilated cardiomyopathy has grown, use of the technique has not decreased but rather has increased in the United States. We recently conducted a survey to determine how widespread the use of endomyocardial biopsy is in the medical community. We sent a questionnaire to all cardiac catheterization laboratories in the United States listed by the Society of Cardiac Angiography.1 We excluded from our analysis laboratories at cardiac transplantation centers as well as the 23 laboratories used by investigators in the Myocarditis Treatment Trial (see below). These groups were excluded because we wished to estimate the incidence of clinical application of endomyocardial biopsy for diagnosis in patients with unexplained congestive heart failure in the community. Sixty percent of 821 laboratories responded, which probably represents only a quarter of the catheterization laboratories now functioning in the United States. Sixty-three percent of the responding laboratories indicated that 6,292 endomyocardial biopsies were performed (22 per laboratory) in 1987 by 734 cardiologists. (At an estimated average of only nine biopsies performed by each cardiologist per year, some may have difficulty in acquiring and maintaining procedural skills.) We estimate from this data and from data we are collecting in the Myocarditis Treatment Trial that at least 20,000 endomyocardial biopsies were done in the United States in 1987 for indications other than monitoring of transplant rejection. To put this data in perspective, we estimate that there are 11,000 new cases of idiopathic, dilated cardiomyopathy per year in the United States, based on annual incidence of four cases per 100,000 population.2

Evidence continues to appear in the literature of a low incidence of specific, therapeutically relevant diagnostic information obtained by cardiac biopsy in patients with heart disease of unknown cause. Publications are often enthusiastic regarding use of biopsy, but careful analysis shows little basis for enthusiasm. For example, Leatherbury and colleagues3 concluded that biopsy performed in 20 pediatric patients was clinically useful in 75%. In nine of their patients, a diagnosis of dilated cardiomyopathy was made on biopsy. However, this is a clinical diagnosis; histopathologic findings are nonspecific. Myocarditis was diagnosed in four, but there is no evidence to date that this disorder can be successfully treated. Two patients had a biopsy diagnosis of hypertrophic cardiomyopathy, both of whom had a clinical diagnosis of dilated cardiomyopathy. Hypertrophy is commonly found in biopsy specimens of patients with dilated cardiomyopathy; the finding on biopsy of hypertrophy is not diagnostic of hypertrophic cardiomyopathy. Four patients had normal results from biopsies, which is not an unusual or particularly helpful observation in patients with overt heart failure. Finally, one patient had histologic evidence for cardiac sarcoidosis. This is treatable.4 Thus, biopsy led to specific, proven therapy in only one patient (5%). Fast and colleagues5 reported on 25 patients who underwent left ventricular endomyocardial biopsy. They made a specific diagnosis in six patients. The potential for proven, specific therapy existed in one (4%). French and coworkers6 reported on 25 patients, 13 of whom had normal left ventricular ejection fraction. A specific myocardial disease was diagnosed in seven patients. This was an unusual group in that six of the seven specific diagnoses were amyloidosis, found in two of the 12 patients with left ventricular dysfunction and in four of the 13 patients with normal left ventricular ejection fraction. The seventh diagnosis was endocardial fibroelastosis, also in the latter group. The investigators suggest that biopsy

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has a higher yield in patients without left ventricular failure. Although they may be correct, none of the patients in this report had a biopsy-detected myocardial disorder for which proven therapy exists.

Admittedly, as viewed above, these data underestimate the overall usefulness of cardiac biopsy because biopsy results that are diagnostically negative, or results that reveal an untreatable disorder, are useful in some cases, and application of biopsy to highly selected populations can increase therapeutically relevant yield. The purpose of reviewing these statistics is to reemphasize the known facts that specific diagnoses, especially ones that lead to specific therapy, are made infrequently by endomyocardial biopsy in the general population of patients with heart muscle disease of uncertain cause, a population that is dominated by patients with idiopathic dilated cardiomyopathy. Why, then, is the use of biopsy pervasive and increasing?

Technique

Improvements in the technique of endomyocardial biopsy cannot explain its increasing clinical use because only small changes have occurred in the past decade. Until recently, the Stanford biopomt, inserted through the right internal jugular vein, was used by most cardiologists in the United States. Long, flexible biopomtes with preformed guiding sheaths are now available for femoral venous insertion. This approach is preferred by many invasive cardiologists accustomed to femoral arterial access for coronary angiography. In addition, disposable biopomtes have been developed that eliminate the need for cleaning, sharpening, and resterilization of the instrument, but which increase the cost of performing biopomtes in laboratories with more than 10 cases a year. A disposable pediatric bipomte is now commercially available.

Although fluoroscopy remains the most common imaging modality to guide biopsy sampling, two-dimensional echocardiography has been used because of its convenience and ability to accurately localize the intracardiac position of the biopomte.

None of these modifications has improved safety or quality of tissue sampling, but they have made the method more available and attractive to invasive cardiologists.

Diagnoses

A few additions can now be made to the list of diseases that can be identified by endomyocardial biopsy (Table 1). These five interesting new diagnoses bring the total to 26 diseases. Unfortunately, patients with these new diagnoses and the other specific diagnoses to which they are added constitute only a small proportion of those with cardiomyopathy.

Indications

The list of validated indications for endomyocardial biopsy (Table 2) has not been expanded. Only

### Table 1. Specific Diagnoses Made by Endomyocardial Biopsy*

<table>
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<tr>
<th>Diagnosis</th>
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<tr>
<td>Cardiac allograft rejection</td>
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<td>Myocarditis</td>
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<tr>
<td>Giant cell myocarditis</td>
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<tr>
<td>Doxorubicin cardiotoxicity</td>
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<tr>
<td>Cardiac amyloidosis</td>
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<tr>
<td>Cardiac sarcoidosis</td>
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<tr>
<td>Cardiac hemochromatosis</td>
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<tr>
<td>Endocardial fibrosis</td>
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<tr>
<td>Endocardial fibroelastosis</td>
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<tr>
<td>Fabry’s disease of the heart</td>
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<tr>
<td>Carcinoid disease</td>
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<tr>
<td>Irradiation injury</td>
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<tr>
<td>Glycogen storage disease</td>
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<tr>
<td>Cardiac tumors of cardiac origin</td>
</tr>
<tr>
<td>Cardiac tumors of noncardiac origin</td>
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<tr>
<td>Kearns-Sayre syndrome</td>
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<tr>
<td>Cytomegalovirus infection</td>
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<td>Toxoplasmosis</td>
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<tr>
<td>Henoch-Schoenlein purpura</td>
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<td>Rheumatic carditis</td>
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<td>Chagasic cardiomyopathy</td>
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<tr>
<td>Chloroquine cardiomyopathy</td>
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<tr>
<td>Lyme carditis</td>
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<tr>
<td>Carnitine deficiency cardiomyopathy</td>
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<tr>
<td>Right ventricular lipomatosis</td>
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<tr>
<td>Hypereosinophilic syndrome</td>
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*Italicized diagnoses are new entries with corresponding citations. *Modified from Table 1 of Mason.

### Table 2. Indications for Endomyocardial Biopsy

<table>
<thead>
<tr>
<th>Type</th>
<th>Indications</th>
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<tbody>
<tr>
<td>Definite</td>
<td>Monitoring of cardiac allograft rejection, Monitoring of anthracycline cardiotoxicity</td>
</tr>
<tr>
<td>Possible</td>
<td>Detection and monitoring of myocarditis, Diagnosis of secondary cardiomyopathies</td>
</tr>
<tr>
<td>Uncertain</td>
<td>Unexplained, life-threatening ventricular tachyarrhythmias, Acquired immune deficiency syndrome, Formulation of prognosis in idiopathic dilated cardiomyopathy</td>
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toxicity of new anthracycline antibiotics.22 This is the second of two generally accepted indications.

Indications listed in Table 2 as “possible” are frequently used, but we do not consider them to be unequivocally validated. The use of biopsy in myocarditis is discussed at length below. We do not consider it appropriate to routinely perform a biopsy in search of one of the secondary cardiomyopathies, such as amyloidosis, because their incidence is low, and effective therapies are available for only a few. There are instances, of course, in which the occurrence of one of the treatable disorders is very likely or the need to exclude one of them is great, justifying performance of a cardiac biopsy. Recently, Schoenfeld et al23 examined the usefulness of cardiac biopsy to aid in differentiation between restrictive and constrictive heart disease. Those investigators found the technique useful in that it identified a specific cause for myocardial restriction in 39% of patients in whom thoracotomy “was contemplated.” Nevertheless, we consider this indication “possible” rather than “definite” because contemplation of surgery does not mean that the correct decision to undertake or forego surgery could not have been made without biopsy. In addition, at least two new noninvasive methods that were not used by the investigators, computed tomography and magnetic resonance imaging of the chest, are helpful in accurately identifying pericardial thickening. Endomyocardial biopsy is undoubtedly useful in some patients considered for thoracotomy, but to what extent its use will be obviated by other techniques is not yet clear.

Three indications in Table 2 are labeled “uncertain.” These are potential indications for cardiac biopsy that are not yet well supported by evidence in the literature. There are six recent reports of 10 or more patients with ventricular tachyarrhythmias who did not have structural heart disease.24-29 They had a strikingly high incidence of histologic myocardial abnormalities: 89% in a total of 75 patients who underwent biopsy. We suspect that the true incidence of abnormalities may be lower. Perhaps the most important observation made by these investigators was the presence of myocarditis in 20% of the patients. Corroboration of these data is needed. If the true incidence of myocarditis in patients with unexplained arrhythmias approaches 20%, endomyocardial biopsy would be indicated in such patients, even if an effective therapy of myocarditis does not exist. Because myocarditis can spontaneously resolve, some patients could be spared the extraordinarily rigorous diagnostic and therapeutic interventions required for control of ventricular tachyarrhythmias.

Recent studies30-33 show that myocarditis may occur in approximately 50% of patients during the course of acquired immune deficiency syndrome. Although the causes of myocarditis are not yet well established in this population, myocarditis is the presumed cause of cardiac failure in a substantial minority. At least one patient has apparently responded to immunosuppressive therapy, despite preexisting lymphopenia.34 Detection and treatment of myocarditis could be helpful in some patients with acquired immune deficiency syndrome, but more information on this subject is required.

It is a useful exercise to review those diagnoses that can be made on endomyocardial biopsy for which there is a specific, proven therapy (Table 3). Only the first six diagnoses in Table 3 usually require an endomyocardial biopsy before therapy can be instituted. The other diagnoses often can be made accurately on the basis of other clinical data. The first four diagnoses are treated with immunosuppression.4,19,20,35,36 Endocardial fibrosis can be treated surgically, both by valve replacement or repair and by endocardial excision.37 Anthracycline cardiotoxicity is prevented by discontinuation of the drug. Although other techniques can be used to detect hemodynamically significant adriamycin-induced toxicity, biopsy is capable of showing the lesion before it is clinically detectable. Treatment of cardiac hemochromatosis can be monitored by biopsy, but biopsy data are not required for institution and completion of successful therapy. The last four entities in Table 3 are treated by specific interventions but are usually evident and readily diagnosed without endomyocardial biopsy. Overall, only the first listed diagnosis is common, but it is managed in a small number of specialized centers. The other treatable diagnoses that require cardiac biopsy are rare and certainly do not justify widespread use of endomyocardial biopsy.

### Myocarditis

The question remains: why is use of cardiac biopsy so prevalent? The desire to diagnose myocarditis may be largely responsible. Interest in making this diagnosis is stimulated by the unconfirmed bias that immunosuppressive therapy is helpful in myocarditis. The first 52 telephone contacts that we had with practicing cardiologists on starting the open enrollment phase of the Myocarditis Treat-
ment Trial (see below) document this bias: 16% of the callers had initiated immunosuppressive therapy even before having histologic confirmation of the diagnosis. We have received numerous additional informal contacts concerning patients with myocarditis. In most of these, the question asked is not “Should I give immunosuppression?” but, rather, “What’s the dose?” Current knowledge does not justify this approach. Anecdotal data and the appealing rationale that myocarditis is an immunologically mediated disorder, which would be expected to respond to immunosuppression, account for the bias. But, there is no scientifically sound data that prove the hypothesis that immunosuppression improves outcome in the general population of patients with myocarditis. The significance of observed improvement coincident with immunosuppressive therapy is completely obscured by the observation of spontaneous improvement in untreated patients. Even if the frequency and extent of spontaneous improvement is less than that induced by immunosuppressive therapy, adverse effects of the latter could outweigh its benefit.

The Myocarditis Treatment Trial is an international study of the efficacy of immunosuppression in myocarditis sponsored by the National Heart, Lung, and Blood Institute (Figure 1). Patients with suspected myocarditis undergo endomyocardial biopsy, and the histologic findings are reviewed by a member of the trial’s pathology panel. If myocarditis is diagnosed and if the patient has a left ventricular ejection fraction less than 0.45, the patient is eligible for randomization to one of two treatments: 1) immunosuppression with cyclosporine and a small prednisone dose, or 2) conventional therapy for congestive heart failure without immunosuppression. In addition to the ejection fraction determination by radionuclide ventriculogram, maximum treadmill exercise time is used to monitor effects of therapy. Assigned therapy is maintained for 6 months. Six months later, at 1 year after diagnosis, final assessment of the patient’s cardiac functional status is performed.
Through September 1, 1988, 1,378 biopsies had been performed at 23 enrolling centers in the trial to rule out myocarditis. Myocarditis was detected in 139 patients (10%). The incidence of myocarditis appears to have decreased.53,54 A recent analysis suggests that this decrease reflects the natural periodicity of enteroviral infections. Pallansch,55 analyzing the periodicity of enteroviral isolates reported to the Centers for Disease Control, has noted that nonpolio enterovirus isolates peak at 3- to 5-year intervals, and the highest prevalence occurred in 1971–1973, 1978–1980, and 1982–1984. In 1988, there was a 40% decrease in reported cases of aseptic meningitis compared with the previous 5-year average. Coxsackievirus B isolates have also declined dramatically. In 1972, more than 1,500 Coxsackievirus B isolates were reported to the Centers for Disease Control; in 1987, this had decreased to slightly more than 100 (personal communication, Mark A. Pallansch). These viruses tend to recur with epidemic periodicity; hence, an increase in the incidence of active myocarditis in the near future is likely. A higher incidence of myocarditis may increase the proportion of biopsies with positive results, and this higher proportion may be especially evident in geographic regions beset by viral epidemics.

Physicians in the United States and Canada may now enroll patients into the Myocarditis Treatment Trial without referral to one of the 23 formal enrollment centers. The purpose of open enrollment is to maximize patient referral, particularly in areas where epidemics may develop and where referral to an enrollment center is not feasible. Data collection through the open enrollment process is simplified (see Appendix).

Some investigators have complained that the histopathologic diagnosis of myocarditis cannot be agreed on,56,57 and one investigator57 has even suggested that treatment of the disorder cannot be tested because the diagnosis cannot be made. In the study by Shanes and colleagues,56 seven pathologists with differing opinions regarding the histopathologic diagnosis of myocarditis independently interpreted slides of variable technical quality to determine whether myocarditis was present. That they disagreed is not surprising. Shanes and colleagues56 suggested that a uniform set of criteria was needed. Though Lie57 doubted that a diagnosis of myocarditis can be agreed on, he acknowledged the existence of a criterion set (the Dallas criteria58). However, he stated that the pathologists who established the criteria continue to use their own independent, contradictory criteria. In fact, the Dallas criteria are used by a panel of seven pathologists in the Myocarditis Treatment Trial and have yielded excellent agreement. On the basis of data from the most recent review of Trial slides by this group, we have calculated a probability of only 3% that one of them would make a diagnosis of myocarditis that was not agreed on by consensus of the panel.

Table 4. New Analyses of Endomyocardial Biopsy Tissue

<table>
<thead>
<tr>
<th>Analysis</th>
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<tr>
<td>Lymphocyte subtyping with monoclonal antibodies</td>
<td>59-63</td>
</tr>
<tr>
<td>Culture of lymphocytes</td>
<td>64-66</td>
</tr>
<tr>
<td>MHC antigen detection with monoclonal antibodies</td>
<td>67,68</td>
</tr>
<tr>
<td>Viral genome detection using in vitro hybridization</td>
<td>69,71</td>
</tr>
<tr>
<td>mRNA quantitation</td>
<td>72</td>
</tr>
<tr>
<td>β-Receptor quantitation</td>
<td>73</td>
</tr>
<tr>
<td>Adenine nucleotides and metabolite quantitation</td>
<td>74,75</td>
</tr>
<tr>
<td>Adenylate cyclase activity</td>
<td>76</td>
</tr>
<tr>
<td>Norepinephrine content</td>
<td>77</td>
</tr>
<tr>
<td>Metabolic pathway activity</td>
<td>78</td>
</tr>
<tr>
<td>Enzyme activities</td>
<td>79</td>
</tr>
<tr>
<td>Actin, myosin, and other polypeptides quantitation</td>
<td>80</td>
</tr>
<tr>
<td>Isolation of single myocardial cells</td>
<td>81</td>
</tr>
<tr>
<td>Sarcoplasmic reticulum function</td>
<td>82,83</td>
</tr>
</tbody>
</table>

MHC, major histocompatibility complex.

Our present recommendation is that biopsy be performed in patients suspected of having myocarditis because of recent onset of unexplained congestive heart failure under only two conditions: 1) the patient is to be enrolled in the Trial if results from the biopsy are positive, or 2) the patient shows progressive deterioration and has such an immediately poor prognosis that any potentially beneficial therapy, even with associated risk, should not be withheld. Although we would prefer that patients of this latter description be randomized in the Trial, we consider it ethical to attempt immunosuppression as a last resort if randomization is not possible. In keeping with this belief, the Trial permits withdrawal of nonimmunosuppressed patients to receive immunosuppression if their condition deteriorates severely.

Future: New Analyses

The usefulness of immunosuppression in myocarditis should be the primary determinant of the appropriate extent of use of endomyocardial biopsy during the next 5 years, outside of its application in cardiac transplantation. All other recognized indications are infrequent. The more distant future of the technique lies in the newly conceived, fascinating analyses that can be applied to biopsy tissue. As noted previously, what is done with the tissue is what counts. Table 4 lists several promising analytic techniques that have recently been applied to endomyocardial biopsy tissue. The diagnostic and prognostic power of many of these methods could prove to be great. Some are discussed below.

Endomyocardial biopsy tissue can be placed in a culture medium containing interleukin-2 to stimulate reproduction of lymphocytes residing in the tissue.64-66 The cultured cells can then be characterized in a variety of ways, which may provide pathogenic, prognostic, and even therapeutically useful information. For example, Kurnick and colleagues65 used the culture technique to determine the phenotype of lymphocytes in the myocar-
dium of patients with myocarditis. They were able to study the ability of these lymphocytes to produce lymphokines and to kill target cells. Zeeri and colleagues\(^\text{66}\) and Duquesnoy and coworkers\(^\text{66}\) have shown that the ability to propagate T cells in culture from biopsies of cardiac transplant recipients identifies those patients who are or will be experiencing tissue rejection. The cultured lymphocytes are specifically reactive to donor antigens. The potential for growing activated lymphocytes with specific reactivity toward myocardial antigens may shed light on the immunopathogenesis of myocarditis and may lead to the development of clinical trials designed to study the effects of therapy in patients who do not meet the currently rigid histologic criteria.

Two West German groups have used in situ hybridization to detect viral genomes in animal models,\(^\text{69,71}\) and the former group has used this method to quantify total mRNA in surgical cardiac biopsy specimens.\(^\text{72}\) Bowles et al\(^\text{70}\) reported in situ hybridization of Coxackie-B virus-specific RNA sequences in myocardial tissue obtained by biopsy from patients with myocarditis and dilated cardiomyopathy. Fifty-three percent of patients with active or healing myocarditis or dilated cardiomyopathy with inflammatory changes had positive hybridization signals. These results are fascinating but require confirmation. Confirmation would have two immediate implications. First, viral infection may be a common cause of idiopathic dilated cardiomyopathy, and second, in situ hybridization may provide a sensitive marker for viral myocardial disease, which could be therapeutically relevant. Of importance, detectable enteroviral genomes have not been shown to reactivate and disseminate after institution of immunosuppressive therapy in humans. Therefore, the significance of these viral signals in the immunopathogenesis of myocarditis in humans is unknown. These techniques may expand the clinical usefulness of endomyocardial biopsy in the future.

Investigators in Bristow’s laboratory\(^\text{73}\) are able to quantify \(\beta\)-receptors in myocardial biopsy material obtained from humans by radioligand binding. \(\beta\)-Receptor down-regulation is thought to be a cause of reduced responsiveness to circulating catecholamines in patients with congestive heart failure. They showed a correlation between \(\beta\)-receptor density and measures of cardiac performance. \(\beta_1\) and \(\beta_2\) subpopulations can now be quantitatively distinguished. Other receptor mechanisms will be studied quantitatively in the future. The ability to thoroughly characterize a patient’s myocardial receptor status may provide therapeutically useful information.

Several biochemical determinations can now be made on endomyocardial samples despite their small size. Chemicals that have been measured include adenine nucleotides and their catabolites,\(^\text{74,75}\) adenylate cyclase activity,\(^\text{76}\) catecholamines,\(^\text{77}\) metabolic pathway intermediates,\(^\text{78}\) and several polypeptides.\(^\text{80}\) Correlations between myocardial concentrations of these materials and extent of myocardial dysfunction have been drawn. Though these new measurements have not yet led to fundamental insights into disease mechanisms, they may in the future and at the same time may aid in monitoring responses to therapy.

Bustamante and associates\(^\text{81}\) have succeeded by enzymatic digestion in isolating viable single atrial and ventricular myocardial cells from human surgical biopsy specimens similar in size to endomyocardial biopsies. These cells have normal resting potentials and produce normal action potentials in response to electrical stimulation. Isolated cardiocytes can be subjected to a number of analyses that are not possible or as meaningful in intact tissue, such as ion flux determinations, single-cell voltage clamp of specific currents, intracellular perfusion, and studies of contractile activity. Application of these techniques to diseased human tissue may clarify causes of disease as well as mechanisms of therapy.

Limas and colleagues\(^\text{82}\) have measured a reduction in calcium uptake by crude homogenates of endomyocardial biopsies obtained from patients with dilated cardiomyopathy. Recently, Movsesian and coworkers\(^\text{83}\) measured normal calcium uptake by purified sarcoplasmic reticulum prepared from patients with dilated cardiomyopathy and found it to be normal, suggesting that Limas’ observation of reduced uptake resulted from a regulatory defect rather than an abnormality intrinsic to the sarcoplasmic reticulum. Future study of these and other isolated subcellular organelles has considerable promise.

**Summary**

At this time, endomyocardial biopsy has proven validity as a diagnostic method in few circumstances. However, it is overused. In the near term, the extent of its use should be modified by knowledge of its therapeutic relevance in patients with myocarditis. In the long term, numerous new techniques for studying pathophysiology at the subcellular and molecular levels will demand a central role for endomyocardial biopsy in the diagnosis, treatment and fundamental understanding of myocardial diseases. We believe that endomyocardial biopsy will serve as an indispensable link between basic scientists and clinicians in the effort to describe disease mechanisms.

**Appendix: Open Enrollment in the Myocarditis Treatment Trial**

Personnel at the University of Utah complete all data forms. A procedures manual, consent forms, and material for the local institutional review board for research involving human subjects are forwarded to the enrolling physician as soon as a potential enrollee is identified. Personnel at the University of Utah can be reached on a 24 hour-a-day basis for enrollment of patients and ongoing
communication regarding their care through a toll-
free number (800 441-5544). Sanoz Pharmaceuti-
cals supplies cyclosporine to randomized patients at
no cost through our center. We continue to encou-
rage referral of patients to one of the established
enrolling centers because a richer data base is
collected at these centers. A list of the centers and
their principal investigators is available through the
toll-free number above. Cooperation of physicians
throughout North America will lead to a more rapid
determination of the efficacy of immunosuppression
in myocarditis as well as a greater understanding of
the pathogenesis of the disease.

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