The Role of Myocarditis in End-Stage Dilated Cardiomyopathy

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Many patients who undergo cardiac transplantation do so as a result of end-stage dilated cardiomyopathy (DC). Little is known about the causes of this condition, but long-term follow-up studies reveal a high incidence of DC in patients who have had acute viral myocarditis. The following article examines the role of myocarditis as a precursor of DC and discusses the possible etiology of myocarditis—based on animal experiments and clinical studies—as well as methods of diagnosis and treatment. ***(Texas Heart Institute Journal 1987; 14:268-275)***

Key words: Myocarditis; dilated cardiomyopathy; myocardial biopsy; immunosuppressive therapy

DILATED CARDIOMYOPATHY (DC) denotes left ventricular dilatation, with normal wall thickness and abnormal systolic function, in the presence of normal coronary arteries, valves, and pericardium.[1] In other words, the strict clinical definition of the disorder involves no etiologic implications. To date, we know very little about the cause of DC, but we do know that this condition is frequently preceded by myocarditis. The treatment of DC, like that of congestive heart failure, is palliative. It is aimed at the effects (the adverse peripheral vascular and humoral compensatory mechanisms) rather than at the disease itself. Natural history studies reveal that, 2 years after the onset of symptoms, the mortality is 50%.[2] Therefore, many of these patients ultimately undergo cardiac transplantation.

Until a clue to the cause of DC is found, the physician can be little more than a passive bystander. The present report concerns the role of myocarditis as a precursor of end-stage DC. The natural history of myocarditis is outlined, and diagnostic and therapeutic options are discussed.

INCIDENCE AND NATURAL HISTORY OF MYOCARDITIS

Myocarditis is not a single disease but rather is a heterogeneous group of disorders that are reflected in one common physiologic presentation. Table I summarizes the relevant literature and shows the incidence of biopsy-proven myocarditis in patients with cardiomyopathy. From the number of centers involved, one can see that this subject has generated a lot of interest. There is a wide discrepancy in the incidence itself, which ranges from 0% to 67%. This makes one wonder whether these studies

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TABLE I. Biopsy-Proven Incidence of Myocarditis in Patients with Cardiomyopathy (from O'Connell and Mason[20])

Investigators	Location and Date	INCIDENCE (%)	(No.)
Kunkel et al	(Frankfort, 1978)	6%	N = 66
Mason et al	(Stanford, 1980)	2%	N = 400
Noda et al	(Osaka, 1980)	1%	N = 52
Baandrup & Olsen	(London, 1981)	1%	N = 132
Das et al	(Cattuck, India, 1981)	10%	N = 10
Nippoldt et al	(Rochester, 1982)	5%	N = 170
Fenoglio et al	(Columbia, 1983)	25%	N = 135
Hess et al	(Richmond, 1983)	23%	N = 23
Unverferth et al	(Columbus, 1983)	6%	N = 59
Strain et al	(New York, 1983)	26%	N = 64
Parillo et al	(Boston, 1984)	26%	N = 74
Zee-Cheng et al	(St. Louis, 1984)	63%	N = 35
O'Connell et al	(Chicago, 1984)	7%	N = 68
Daly et al	(London, 1984)	17%	N = 69
Bolte and Ludwig	(Munich, 1984)	20%	N = 91
Regitz et al	(Munich, 1984)	6%	N = 299
Rose et al	(Cape Town, 1984)	0%	N = 76
Ruzyllo et al	(Warsaw, 1985)	61%	N = 57
Dec et al	(Boston, 1985)	67%	N = 27
Mortensen et al	(Copenhagen, 1985)	18%	N = 65
Ferriere et al	(Montpellier, France, 1985)	5%	N = 59
Hosenpud et al	(Portland, 1985)	16%	N = 38
Cassling et al	(Omaha and Indianapolis, 1985)	3%	N = 80
Salvi et al	(Trieste, 1985)	18%	N = 74

have involved dramatically different patient populations or wide geographic variations. Closer analysis reveals only slight variation in patient population. Moreover, several of the centers are clustered geographically—for example in the American Midwest, where incidences vary from 3% to 60%. What this variation in incidences probably represents is a lack of consensus among pathologists in interpreting the biopsy results. Owing to the recognition of this discrepancy, a panel of pathologists has agreed to define myocarditis as a primary inflammatory infiltrate, with injury of adjacent myocytes, not due to coronary disease (Fig. 1).[3] If that working definition could be applied and standardized, the literature would be more easily interpretable.

The natural course of myocarditis also varies to an astonishing degree. In 1806, the French pathologist Corvisart made the following observation[4]:

> Hence this inflammation almost always terminates fatally; but the death which it usually occasions may happen instantly or somewhat slowly. Thus *carditis* has been known to become fatal in a very few days; while in other instances, when the disease has attained to its highest degree, the most alarming symptoms partially disappear, and a sort of convalescence is established; sometimes even the patient is restored to apparent health; he then flatters himself with a near and perfect cure; but the most intelligent physician perceives only a transformation, or degeneration of the disease into another affection slower, but not less severe, as a *chronic organic* disease is then established, mortal in all cases.

Corvisart's description is similar to modern accounts of myocarditis, especially with regard to the fact that an infectious agent can produce a chronic, smoldering, inflammatory myocardial reaction that ultimately results in end-stage cardiac disease. Obviously, there was little way to accumulate evidence to support this hypothesis, since an

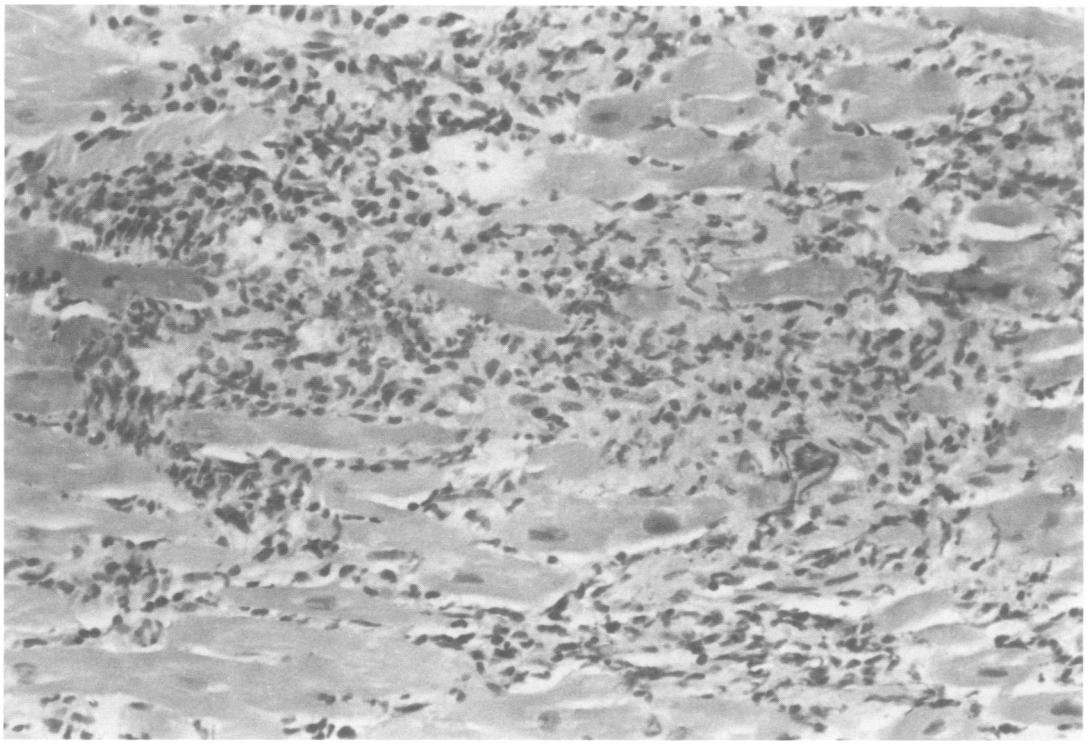

Fig. 1 Photomicrograph of an endomyocardial biopsy specimen from a patient with unexplained congestive heart failure. The specimen shows a lymphomononuclear infiltrate, with myocyte necrosis, indicating active myocarditis (hematoxylineosin; original magnification, 20x). From O'Connell et al.[19]

early nineteenth-century pathologist could hardly have reached this conclusion on the basis of autopsy findings. Even today, it is almost impossible to establish such a conclusion, since the viral infections that lead to myocarditis are quite common. At least 70% of the general population has been exposed to cardiotropic viruses, and no doubt half have had an episode of acute viral myocarditis, which was subclinical in the vast majority.

For these reasons, it is impossible to pinpoint everyone who has a viral syndrome and subject him to a biopsy in order to diagnose the disease and elucidate its natural history. Nevertheless, some important insights can be gained from animal models.

Animal Experiments

If a weanling mouse is given Coxsackie B3 virus, which is the most commonly recognized cause of human viral myocarditis, the virus will replicate within the myocardium for 7 to 9 days.[5] Viral clearance is mediated by B lymphocytes, interferon, and macrophages. Cellular infiltrates are not encountered during this period. If the mouse is pretreated with either cyclophosphamide or corticosteroids—which grossly affect the humoral immune responses—it will die of a disseminated viral infection. If it is pretreated with bone marrow radiation, reconstitution, and thymectomy or antithymocyte serum (two established methods that will eliminate T-cell responses while preserving B-cell responses), the acute phase of the illness will continue unabated. Cellular immune responses, therefore, play very little role in viral clearance, which occurs independently of the inflammatory reaction that is seen histologically.

After the ninth day, the virus can no longer be cultured. If the T-cell responses are eliminated with one of the methods described above, the chronic phase is markedly decreased. If the mouse is killed 6 months later, the histologic findings (hypertrophy and fibrosis with persistent inflammation) will be similar to those associated with human lymphocytic myocarditis.[6] At 1 year after infection, symptomatic heart failure develops, and autopsy reveals hypertrophy, fibrosis, and mural thrombi in the

absence of inflammation—findings that are identical to those associated with DC in human beings.[7] In other words, the experiments in mice prove that, even after being cleared from the myocardium, the infective agent induces a progressive cell-mediated immune response, which eventually results in congestive heart failure and death. Terminally, evidence of the inflammatory reaction is missing.

Clinical Studies

In man, obviously the picture is much more sketchy (Table II). As stated earlier, myocarditis remains unsuspected in most of the persons who have it; even when it is suspected, a biopsy cannot be performed in every case. We know, however, that the antibody titers to the enteroviruses, which are primarily responsible for many clinical cases of human myocarditis, are elevated in patients with DC.[8] Follow-up (6-year) studies in patients with nasopharyngeal isolation of Coxsackie B virus in the absence of clinical acute myocarditis show that 10% have cardiac symptoms or electrocardiographic abnormalities.[9] Long-term follow-up studies also reveal a high incidence of DC in patients who recover from acute viral myocarditis (Table III). Because these patients have clinically recognizable, acute viral myocarditis, we must assume that they have a more serious form of the disease than average. Long-term follow-up reveals that the incidence of DC after recovery from myocarditis is approximately 12%. Conversely, the incidence in the general population is about five to eight new cases per 100,000 persons per year.[10] Therefore, the incidence of DC in patients who have had acute viral myocarditis is several orders of magnitude greater than that in the general population.

If numerous people contract myocarditis, why do only a handful, or 10%, subsequently develop cardiomyopathy? Perhaps one clue is furnished by the work of Fowles and associates,[11] who found that many patients with DC had a suppressor lymphocyte functional defect. In other words, because their immune responses could not be suppressed, they tended to "overreact" to stimuli; therefore, they were more likely to develop a chronic inflammatory reaction. With regard to pathogenesis, then, there appears to be

TABLE II. Evidence Linking Myocarditis to Dilated Cardiomyopathy in Human Beings

- Enteroviral antibody titers are more commonly elevated in cardiomyopathy patients than in control patients.
- Long-term follow-up of patients with culture-positive Coxsackie B noncardiac infections reveals a high incidence of cardiac abnormalities.
- Follow-up of patients with clinical acute viral myocarditis reveals a high incidence of dilated cardiomyopathy.

TABLE III. Incidence of Dilated Cardiomyopathy (DC) after Acute Myocarditis*

Investigator and Date	Total No. of Patients	No. (%) of Patients with DC	Duration of Follow-up
Levander-Lindgren, 1965	154	13 (8%)	7.3 yr
Bengtsson and Lamberger, 1966	90	17 (19%)	5 yr
Sainaini et al, 1968	22	5 (23%)	Unspecified
Bergstrom et al, 1970	15	0 (0%)	1 to 4 yr
Smith, 1970	22	6 (27%)	6 mo to 6 yr
Gerzen et al, 1972	45	0 (0%)	6 to 68 mo
Obeyesekere and Hermon, 1973	32	3 (9%)	Unspecified
Hayakawa et al, 1983	20	6 (30%)	49 mo
TOTAL	400	50 (12.5%)	

*In all cases, the diagnostic modality was clinical.

an acute phase during which active viral replication occurs in the myocardium. This phase, which is short-lived and mainly subclinical, results in the humoral antibody response that eliminates the virus. Certain individuals, however—perhaps those with a defect in immunoregulation—have a cell-mediated autoimmune response. These persons will contract progressive, smoldering myocardial necrosis that culminates in heart failure. By the time idiopathic DC supervenes, the patient may no longer have the inflammation. Ideally, a biopsy should be performed during the active inflammatory stage, before a great deal of damage has been done.

DIAGNOSIS

Biopsy

Until the early 1970s, investigators were unable to routinely evaluate the histology of the living myocardium. The first myocardial biopsy technique popularized in this country was the Stanford method, which involves cannulating the right internal jugular vein and advancing the bioptome towards the apical septal portion of the right ventricle, where tiny fragments of tissue are removed.[12] These samples usually measure between 2 and 3 mm in maximum diameter. For the diagnosis of myocarditis, four to six fragments are necessary. The diagnosis is based on evidence of an inflammatory reaction, with myocyte damage, in the absence of coronary artery disease.

This technique was applied for the first time in patients with unexplained congestive heart failure by Mason and associates,[13] who started performing myocardial biopsies in patients without coronary artery disease who had been referred to Stanford's heart transplant program. In ten cases, they found evidence of what was called "inflammatory myocarditis;" when prednisone and azathioprine therapy was instituted, some patients showed improvement.

In performing a biopsy, the physician is trying to assess the condition of an 800-g heart on the basis of 15 mg of tissue. Therefore, if myocarditis is a focal process (and there is some evidence that it is), sampling errors may cause the diagnosis to be missed. At this time, we have no way of knowing the sensitivity of biopsy unless the disease results in death or transplantation, after which the explanted heart can be evaluated.

With respect to clinical presentation, when 14 patients with biopsy-proven myocarditis were compared to 109 patients without this condition, the hemodynamics of the two groups showed little difference.[14] As Table IV shows, the only statistically significant difference between the two groups

TABLE IV. Clinical and Hemodynamic Comparison of Patients with and without Biopsy-Proven Myocarditis (from O'Connell et al[14])

	Bx+	Bx−
Number of patients	14	109
Age (yr)	38.9 ± 16.8*	46.4 ± 14.5
Sex (M/F)	11/3	74/35
CI III-IV CHF	11 (78%)	81 (74%)
CI (l/min/m^2)	2.3 ± 0.7	2.6 ± 0.7
PAW (mm Hg)	17.4 ± 8.8	19.1 ± 10.0
PA_{sys} (mm Hg)	37.1 ± 15.8	42.4 ± 15.4
LVEDD (cm)	6.2 ± 0.8**	6.9 ± 1.0
EF (%)	17.5 ± 8.0	17.8 ± 8.4

*Mean ± standard deviation

**$p<0.01$

Bx+ = biopsy-proven myocarditis; Bx− = biopsy negative for myocarditis; CI = cardiac index; CI III-IV CHF = symptomatic heart failure, New York Heart Association class III or IV; EF = ejection fraction; F = female; LVEDD = left ventricular end-diastolic dimension; M = male; PA_{sys} = pulmonary arterial systolic pressure; PAW = mean pulmonary artery wedge pressure.

Table V. Immunosuppression in Biopsy-Proven Myocarditis: Uncontrolled Studies

Author	Location, Date	No. of Pts	No. (%) Improved
Mason et al	(Stanford, 1980)	10	5 (50%)
Sekiguichi et al	(Tokyo, 1980)	3	2 (67%)
Edwards et al	(Rochester, 1982)	4	2 (50%)
Fenoglio et al	(New York, 1983)	19*	8 (42%)
Hess et al	(Richmond, 1983)	6	6 (100%)
Daly et al	(London, 1984)	9	7 (78%)
Fenely et al	(Sydney, 1984)	2	2 (100%)
Vignola et al	(Miami Beach, 1984)	6	5 (83%)
Zee-Cheng et al	(St. Louis, 1984)	11	5 (45%)
Dec et al	(Boston, 1985)	9	4 (44%)
Hosenpud et al	(Portland, 1985)	6	0 (0%)
Mortensen et al	(Copenhagen, 1985)	12	8 (67%)
	TOTAL	97	54 (56%)

*Data from "acute," "rapidly progressive," and "chronic" classifications have been pooled.

TABLE VI. Incidence of Spontaneous Improvement in Biopsy-Proven Myocarditis

Author	Location, Date	No. of Patients	No. (%) Improved
Sekiguchi et al	(Tokyo, 1980)	9	7 (78%)
Edwards et al	(Rochester, 1982)	6	3 (50%)
Dec et al	(Boston, 1985)	18	6 (33%)
	TOTALS	33	16 (48%)

was that the patients with active myocarditis had smaller left ventricles. This may have been related to the duration of the symptoms, which was slightly shorter in this group. From a clinical standpoint, there are few ways of discriminating between patients with active myocarditis and those without. When a patient presents with heart failure of recent onset (<2 years), the clinician cannot tell, just by looking at the patient, whether or not a biopsy sample will reveal histologic evidence of myocarditis.

Noninvasive Imaging Techniques

Noninvasive imaging techniques may be useful in diagnosing this condition. Gallium 67 scanning, a technique used to identify chronic inflammatory disease in other organ systems, has recently been applied to the myocardium.[15] In preliminary studies, a positive gallium scan improved the diagnostic yield of biopsy fourfold (baseline incidence of myocarditis, 8%; incidence associated with a positive scan, 36%). Because this technique has been applied in only small numbers of cases, however, its sensitivity and specificity cannot yet be calculated. Yasuda and colleagues,[16] at Massachusetts General Hospital, have recently described indium lll antimyosin antibody imaging. Gallium is an inflammatory-avid isotope, whereas antimyosin antibodies are capable of labeling myocytes. Because histologic myocarditis consists of active inflammation in the presence of myocyte necrosis, indium 111 antimyosin antibodies may be useful in detecting this condition. Again, since this technique has been applied in only a small number of patients, it cannot yet be recommended as a diagnostic modality.

TREATMENT

The impact of accurate diagnosis lies in the following question: If histologic evidence of myocarditis is found, can anything be done to change the natural history of the disease? As a follow-up to the work of Mason and associates,[13] who initiated the use of immunosuppression in these cases, immunosuppressive agents have been used to treat 97 patients with DC and biopsy-proven myocarditis (Table V). The regimens incorporated the use of steroids alone or combined with azathioprine; antithymocyte globulin (ATG); and, more recently, cyclosporine. Of the 97 patients, 54 improved, for a 56% success rate. At face value, this form of therapy appears quite promising, since it improves survival. As a matter of fact, however, the literature reveals only 33 patients with biopsy-proven myocarditis who have not been immunosuppressed (Table VI); surprisingly, 48% of them improved anyway. Therefore, two questions are paramount: Does biopsy identify a group of patients who are going to improve simply because they have myocarditis? Does the rate of spontaneous remission equal the rate of improvement seen with immunosuppressive therapy?

Moreover, the attendant morbidity of these medications must be borne in mind. Hosenpud and co-workers[17] are the only investigators who have underlined the adverse effects of this therapy: In three of six patients on a regimen of prednisone and azathioprine, they detected significant side effects without substantial improvement. Obviously, the cost-benefit ratio of immunosuppression needs further elucidation.

Additional controversies stem from the fact that myocarditis may remit spontaneously; histologic improvement may occur, without improvement in function; clinical improvement may occur in the absence of histologic resolution. On the other hand, some myocarditis patients at death's door have responded dramatically to immunosuppressive agents. Although these drugs may have an appropriate role in treating the disease, that role cannot be precisely defined until controlled studies can be performed.

As a result of these dilemmas, several centers are cooperating, with NIH support, in order to test the hypothesis that immunosuppressive therapy is an efficacious form of treatment for biopsy-proven myocarditis. This nationwide effort, which is being coordinated by the University of Utah, includes 22 enrollment centers throughout the United States and one center in Canada. It also includes a humoral immunology laboratory at Johns Hopkins University and a cellular immunology laboratory at the University of Nebraska. The investigation has three aspects: (1) a clinical trial, which proposes to determine whether immunosuppressive therapy can benefit patients with myocarditis; (2) a cellular immune trial, intended to characterize the roles of lymphocyte subtypes in the pathogenesis of human myocarditis; and (3) a humoral immune study, designed to identify the myocardial antigens recognized by the autoantibodies in human beings.

Essentially, patients with unexplained congestive heart failure and biopsy-proven myocarditis who have consented to the study will be randomized into one of three groups: (1) those who receive conventional therapy for congestive heart failure alone; (2) those who are given conventional therapy plus prednisone and azathioprine; and (3) those who receive conventional therapy plus prednisone and cyclosporine. After being treated for 6 months with one of these immunosuppressive regimens, the patients will be followed up for another 6 months. Final evaluation of their cardiac function will be performed 1 year after the original biopsy. Assessments of the efficacy of treatment will be based primarily on left ventricular ejection fraction at rest (as evaluated by radionuclide techniques) and during maximum exercise. It is impossible to base heart failure studies on a single parameter alone, since a patient can either feel well and have poor results or can feel ill and have good results. Therefore, both parameters must be examined in order to tell whether or not the therapy is successful. Secondary end points include survival, serial histologic studies, arrhythmia, and symptoms.

The results of this trial will likely define the natural history of biopsy-proven myocarditis and ascertain the efficacy of immunosuppression. They will have a major impact on the way in which myocardial biopsy is used.[18] If immunosuppression alters the natural history of myocarditis, all patients with unexplained heart failure should undergo biopsy to rule out myocarditis. If immunosuppression does not alter the natural history, the clinical use of biopsy should be restricted to cardiac transplant and oncology centers where allograft rejection and anthracycline cardiotoxicity must be evaluated.

REFERENCES

1. Report of the WHO/ISFC Task Force on the definition and classification of cardiomyopathies. Br Heart J 1980; 44: 672-673.
2. Fuster V, Gerson BJ, Giuliani ER, Tajik AJ, Brandenburg RO, Frye WL. The natural history of idiopathic dilated cardiomyopathy. Am J Cardiol 1981; 47:525-531.
3. Aretz HT, Billingham ME, Edwards WS, Factor SM, Fallon JT, Fenoglio JJ, Jr, Olsen EGJ, Schoen FJ. Myocarditis: A histopathologic definition and classification. Am J Cardiovasc Pathol 1987; 1:3-14.
4. Corvisart JN. Quoted in Sanders V. Viral myocarditis. Am Heart J 1963; 66:708.
5. Woodruff JF. Viral myocarditis: A review. Am J Pathol 1980; 101:427-479.
6. Wilson FM, Miranda Q, Chason J, Lerner AM. Residual pathologic changes following murine Coxsackie A and B myocarditis. Am J Pathol 1969; 55:153-164.
7. Reyes MP, Khang-Loon H, Smith F, Lerner AM. A mouse model of dilated-type cardiomyopathy due to Coxsackie virus B3. J Infect Dis 1981; 144:232-236.
8. Cambridge G, MacArthur CGC, Waterson AP, Goodwin JF, Oakley CM. Antibodies to Coxsackie B viruses in congestive cardiomyopathy. Br Heart J 1979; 41:692-696.
9. Orinies E. The late cardiac prognosis after Coxsackie B infection. ACTA Med Scand 1968; 183:235-237.
10. Torp A. Incidence of congestive cardiomyopathy. Postgrad Med J 1978; 54:435-437.
11. Fowles RE, Bieber C, Stinson E. Defective in vitro suppressor cell function in idiopathic congestive cardiomyopathy. Circulation 1979; 59:483-491.
12. Mason JW. Techniques for right and left ventricular endomyocardial biopsies. Am J Cardiol 1978; 41:887-892.
13. Mason JW, Billingham ME, Ricci DR. Treatment of acute inflammatory myocarditis assisted by endomyocardial biopsy. Am J Cardiol 1980; 45:1037-1044.
14. O'Connell JB, Robinson JA, Gunnar RM, Scanlon PJ. Clinical aspects of virus/immune myocarditis. Heart Vess Suppl 1985; 1:102-106.
15. O'Connell JB, Henkin RE. Myocardial gallium-67 imaging in dilated cardiomyopathy. Postgrad Med J 1985; 61:1132-1135.
16. Yasuda T, Palacios IF, Dec GW, Fallon JT, Gold HK, Leinback RC, Strauss HW, Khaw BA, Haber E. Indium-111 monoclonal antimyosin imaging in the diagnosis of acute myocarditis. Circulation 1987; 76:306-311.
17. Hosenpud JD, McAnulty JH, Niles NR. Lack of objective improvement in ventricular systolic function in patients with myocarditis treated with azathioprine and prednisone. J Am Coll Cardiol 1985; 6:797-801.
18. Mason JW. Endomyocardial biopsy: The balance of success and failure. Circulation 1985; 71:185-188.
19. O'Connell JB, Gunnar RM. Dilated congestive cardiomyopathy: Prognostic features and therapy. J Heart Transplant 1982; 2:7-17.
20. O'Connell JB, Mason JW. The roles of endomyocardial biopsy and gallium 67 scintigraphy in the assessment and treatment of active endocarditis. In Kawai C, Abelmann WH (eds): *Pathogenesis of Myocarditis and Cardiomyopathy: Recent Experimental and Clinical Studies*. Tokyo, University of Tokyo Press (in press).