Medical Progress

Diagnosing and Treating Active Myocarditis

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The treatment of dilated cardiomyopathy is palliative and, hence, has little effect on the natural history. Therapy directed toward the cause rather than the effect will be necessary before mortality can be affected. Active myocarditis is postulated to be the cause of dilated cardiomyopathy in a subset of patients. A model of murine coxsackievirus B3 myocarditis has immunopathogenic parallels to the disease in humans and suggests that persistent autoimmune reactivity following viral clearance leads to progressive myocyte damage and dilated cardiomyopathy. In preliminary uncontrolled studies, patients with myocarditis have shown clinical and histologic improvement with the addition of immunosuppressive therapy, but there may also be a significant rate of spontaneous improvement. A multicenter study currently acquiring patients is designed to determine the efficacy of immunosuppression and the natural history of active myocarditis.

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Dilated cardiomyopathy is an important cause of congestive heart failure, affecting a young population and resulting in death in 50% within two years of diagnosis.[1] The treatment is palliative, designed primarily to alter the deleterious peripheral vascular compensatory mechanisms resulting from organ underperfusion.[2] Because there is no definitive treatment, this disorder remains the most common indication for cardiac transplantation.[3] Dilated cardiomyopathy includes a heterogeneous group of disorders in which myocarditis may be an important etiologic factor. Successful treatment of myocarditis when instituted early in the course of the disease might prevent irreversible myocardial damage.

Myocarditis May Be a Precursor of Dilated Cardiomyopathy

It has been more than 150 years since it was first postulated that an infectious agent *(Corynebacterium diphtheriae)* may elicit an inflammatory response that culminates in chronic myocardial disease.[4] Nevertheless, the ability to establish an accurate diagnosis of myocarditis during life has only recently become possible. Evidence supporting the concept that a viral infection leads to adverse immunologic responses culminating in dilated cardiomyopathy is largely circumstantial in human subjects (Table 1). An animal model has been developed that may shed some light on the human disease.

When coxsackievirus B3, the most commonly proposed etiologic vector of human myocarditis, or encephalomyocarditis virus is injected into selected murine strains, a self-limited infection of the myocardium results.[5] The infective phase is characterized by myocyte viral replication that is halted within seven to ten days after inoculation by interferon, macrophages, natural killer cells, and humoral antibody. During this acute phase, minimal myocyte necrosis is present with sparse inflammatory infiltration. As the virus is eliminated, lymphomononuclear cell infiltration intensifies. Chronic myocardial damage is inflicted by autodirected T lymphocytes in BALB/c and CD1 murine strains and by humoral antibody in DBA/J strains.[6] In the former, the stimulus may be either a fibroblast neoantigen[7] or cross-reactivity between myocyte and viral antigens.[8] In the DBA/J strain where humoral immune responses play a significant role, myosin is thought to be of antigenic importance.[9]

In outbred murine strains infected with coxsackievirus B3, dystrophic mineralization, myocyte hypertrophy, and interstitial fibrosis develop by six months in the presence of active inflammation.[10] By one year following infection, chamber dilatation and mural thrombi occur with histologic features similar to those in human cases of dilated cardiomyopathy.[11] In this advanced stage, inflammation is no longer present. During the early phase of the illness, the animal remains free of signs of congestive heart failure; by the end-stage ascites, peripheral edema and a loss of muscle mass occur as manifestations of chronic congestive heart failure. In summary, in the animal model, viral infection results in autoimmune responses after viral clearance that lead to progressive myocyte destruction, congestive heart failure, and death of the host.

It is easy and perhaps correct to postulate a similar pathogenesis in humans. Despite the large number of patients who have been thoroughly evaluated, including culture of myocardial biopsy specimens, only one adult has been reported to have active myocardial viral infection proved during life.[12] Until recently, the only feasible approach has been to infer active viral infection or a previous exposure to cardiotropic viruses by measuring neutralizing antibody titers. Fletcher and co-workers found a titer greater than 1:40 against coxsackievirus B in 30% of patients with dilated cardiomyopathy and 30% of controls.[13] Cambridge and associates, however, found a titer greater than 1:1,024 in 30% of patients with dilated cardiomyopathy and in only 2% of controls, suggesting that patients with the disorder had had expo-

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sure to cardiotropic viruses more frequently.[14] Eggers and Mertens measured neutralizing antibody titer against five coxsackievirus B serotypes in a normal population and found that by age 60 years, 53% had an elevated titer against at least one serotype, suggesting that exposure to cardiotropic viruses is common and an isolated measure of antibody titer may be meaningless.[15] Recombinant DNA technology and in situ hybridization are recently developed, highly sensitive techniques for detecting viral genomes. Bowles and colleagues developed a coxsackievirus B-specific complementary DNA hybridization probe to identify nucleic acid sequences in endomyocardial biopsy specimens.[16] Of 17 patients with "active" or "healing" myocarditis or "dilated cardiomyopathy with inflammation," 9 had positive hybridization signals, and of 4 biopsy specimens from patients with dilated cardiomyopathy without inflammation, none were positive. Verifying the specificity of the probes is of utmost importance. If sequences of the hybridization probe share similarities to human DNA or RNA sequences, false-positive signals may result. Nonetheless, these data, if confirmed, support the hypothesis that a viral infection leads to myocarditis and ultimately dilated cardiomyopathy.

Follow-up evaluation of patients with oropharyngeal cultures positive for coxsackievirus B was reported by Orinius[17]: 60 patients younger than 35 years had positive cultures in the absence of clinical evidence of myocarditis. Of these, 53 were evaluated six years after the positive culture was obtained and 10 (19%) had cardiac symptoms or electrocardiographic abnormalities. In patients who recovered from myocarditis diagnosed by clinical criteria, the incidence of myocarditis on long-term follow-up was 12% (Table 2).[18-25] Since the incidence of dilated cardiomyopathy in the general population is about 7 new cases per 100,000 population per year,[26] the incidence is significantly greater after documented cardiotropic virus infection or clinically diagnosed myocarditis than in the general population. Quigley and colleagues in Great Britain observed for 56 months 23 patients with biopsy-proved myocarditis.[27] Dilated cardiomyopathy developed in 5 of 16 survivors, 5 patients who died, and 2 who underwent cardiac transplantation. In contrast, Sekiguchi and co-workers observed for as long as five years 30 patients in Japan with acute viral myocarditis and histologic confirmation and noted only 2 survivors (8%) with clinical evidence of dilated cardiomyopathy.[28] The difference between these studies may reflect the differing acuteness of the clinical disease.

Despite the controversies, it is clear that dilated cardiomyopathy develops in some patients with active myocarditis, whereas others recover with no residual cardiac dysfunction. Fowles and associates were the first to describe an immunoregulatory defect in suppressor cell function in patients with this disorder.[29] Eckstein and co-workers confirmed this defect and found similar results in patients with active myocarditis.[30] Although not all such patients have demonstrable defects in immunoregulation, it is attractive to hypothesize that an immunoregulatory defect predisposes to persistent immune responses after cardiotropic virus infection in some patients. If so, the host immunoregulatory milieu may be as important in the development of dilated cardiomyopathy as the infection itself. This possibility may account for the documentation of myocarditis in familial cardiomyopathy[31] and the high frequency of myocarditis in women with peripartum cardiomyopathy.[32]

In summary, circumstantial evidence supports the hypothesis that viral myocardial infection leads to autoimmune responses which culminate in chronic myocyte damage, compensatory hypertrophy, dilated cardiomyopathy, and congestive heart failure.

TABLE 1.—*Evidence of the Role of Myocarditis in Dilated Cardiomyopathy*

Persistent immune responses lead to progressive myocyte damage following viral clearance in a murine model
Patients with dilated cardiomyopathy have exposure to cardiotropic viruses at a greater frequency than controls
Patients who recover from clinically suspected acute viral myocarditis have a higher frequency of dilated cardiomyopathy on long-term follow-up than controls
An immunoregulatory defect in suppressor-lymphocyte function has been documented in patients with myocarditis and dilated cardiomyopathy
Active myocarditis may be seen on biopsy specimens from patients presenting with presumed dilated cardiomyopathy

Diagnosing Myocarditis

Before endomyocardial biopsy began to be used in patients with unexplained heart failure, the antemortem diagnosis of myocarditis was solely dependent on clinical criteria. Congestive heart failure of unknown cause preceded by a viral syndrome with an associated fourfold rise in antibody titer to cardiotropic virus was presumptive evidence of myocarditis, particularly if pericarditis or atrioventricular block was present.[33] Mason and colleagues applied the technique of endomyocardial biopsy to patients with heart failure of unknown cause and identified myocarditis in ten.[34] The

TABLE 2.—*Incidence of Dilated Cardiomyopathy Following Recovery From Clinically Suspected Acute Viral Myocarditis*

Source	Patients, No.	Patients With Dilated Cardiomyopathy, No. (%)	Duration of Follow-up, years
Levander-Lindgren, 1965[18]	154	13 (8)	7
Bengtsson and Lamberger, 1966[19]	90	17 (19)	5
Sainani et al, 1968[20]	22	5 (23)	Unspecified
Bergström et al, 1970[21]	15	0 (0)	4
Smith, 1970[22]	22	6 (27)	6
Gerzēn et al, 1972[23]	45	0 (0)	5
Obeyesekere and Hermon, 1973[24]	32	3 (9)	Unspecified
Hayakawa et al, 1983[25]	20	6 (30)	4
Total	400	50 (12)	

incidence of biopsy-documented myocarditis in patients with unexplained heart failure in subsequent reports has varied widely (Table 3).[35-46] This variation cannot be fully explained by geographic differences in the occurrence of epidemics of cardiotropic viruses. A difference in the pathologic interpretation of biopsy specimens is likely the major cause of this discrepancy.

A panel of cardiac pathologists, highly skilled in interpreting endomyocardial biopsy findings, met to establish a working definition of myocarditis to be used in a large multicenter study.[47] They defined "active" myocarditis as the presence of inflammatory infiltration with injury to adjacent myocytes in the absence of coronary artery disease (Figure 1). It is hoped that the publication of these criteria will stimulate cardiac pathologists to apply them or to strictly define their own criteria so that data from various centers may be accurately compared.

Endomyocardial biopsy may be subject to a sampling error in the detection of myocarditis. Although the incidence of a false-negative diagnosis of cardiac transplant rejection is reduced to 2% if at least four adequate specimens are obtained,[48] the frequency with which the endomyocardial biopsy fails to detect active myocarditis is unknown.

Radionuclide techniques in cases of myocarditis have recently been studied in an effort to obviate the necessity of biopsy. Gallium 67, an inflammation-avid radioisotope, is highly sensitive but nonspecific compared with the gold standard of biopsy.[42] The practical limitations of imaging this isotope and the computer processing required to enhance sensitivity make gallium scanning difficult for wide application as a screening tool. Imaging using a murine antimyosin antibody (Fab) labeled with indium 111 has been applied to detect the myocyte necrosis associated with myocarditis and has shown promise as a screening technique in patients with newly occurring heart failure.[49] This technique is also highly sensitive but nonspecific. It has been suggested that the lack of specificity may be due to sampling error of endomyocardial biopsy rather than nonspecific myocardial uptake of the isotope. Nevertheless, myocardial biopsy remains the standard against which other techniques are compared. Both ^{67}Ga and ^{111}In antimyosin antibody imaging must be studied in large trials to ascertain their clinical usefulness in comparison with that of myocardial biopsy.

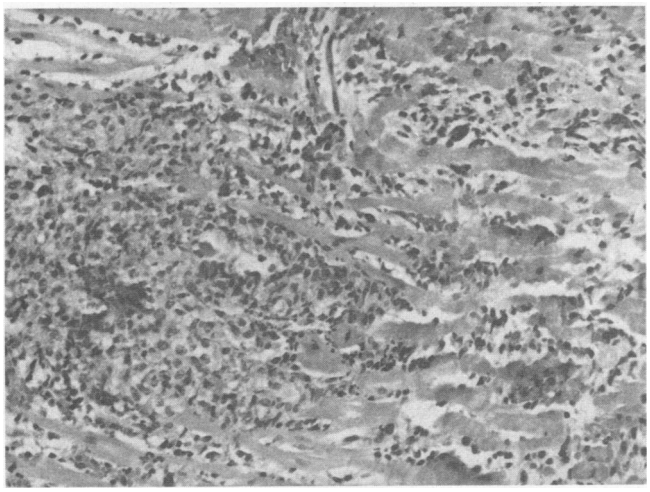

Figure 1.—A photomicrograph of an endomyocardial biopsy specimen from a patient with unexplained congestive heart failure shows a predominantly lymphocytic infiltrate with necrosis of adjacent myocytes compatible with active myocarditis (hematoxylin and eosin, original magnification × 63).

When patients with active myocarditis were compared with those with possible myocarditis but negative results on endomyocardial biopsy, clinical and hemodynamic variables were not useful in predicting the results of the biopsy.[33] Even an antecedent viral syndrome or elevation of erythrocyte sedimentation rate was not a predictor of the histologic findings or prognosis.

Treatment

Mason and associates reported the results of immunosuppressive therapy in biopsy-documented myocarditis.[34] Five of ten patients treated with prednisone alone or in combination with azathioprine improved. Although this result was better than the authors would have expected in untreated patients, they predicted the need for randomized prospective trials to determine the efficacy of therapy. Numerous investigators have subsequently reported their uncontrolled experience with immunosuppressive therapy in biopsy-proved myocarditis using prednisone alone or in combination with azathioprine, antithymocyte globulin, or cyclosporine.

TABLE 3.—*Incidence of Myocarditis in Patients With Unexplained Congestive Heart Failure*

Source	Location	Patients With Biopsies, No.	Patients With Myocarditis, No. (%)
Mason et al, 1980[34]	Stanford, Calif	400	10 (2)
Nippoldt et al, 1982[35]	Rochester, Minn	34	4 (12)
Fenoglio et al, 1983[36]	New York	135	34 (25)
Hess et al, 1983[37]	Richmond, Va	23	6 (26)
Unverferth et al, 1983[38]	Columbus, Ohio	42	4 (10)
Strain et al, 1983[39]	New York	64	17 (26)
Parillo et al, 1984[40]	Boston	74	19 (26)
Zee-Cheng et al, 1984[41]	St Louis	35	22 (63)
O'Connell et al, 1984[42]	Chicago	68	5 (7)
Dec et al, 1985[43]	Boston	27	18 (67)
Hosenpud et al, 1985[44]	Portland, Ore	38	6 (16)
Cassling et al, 1985[45]	Omaha, Neb, and Indianapolis, Ind	80	2 (2)
French et al, 1986[46]	Los Angeles	25	0 (0)
Total		1,045	147 (14)

TABLE 4.—*Response of Biopsy-Proved Myocarditis to Immunosuppression in Uncontrolled Trials**

Source	Location	Patients	
		Treated, No.	Improved, No. (%)
Mason et al, 1980[34]	Stanford, Calif	10	5 (50)
Sekiguchi et al, 1980[50]	Tokyo	3	2 (67)
Edwards et al, 1982[51]	Rochester, Minn	4	2 (50)
Fenoglio et al, 1983[36]	New York	19	8 (42)
Hess et al, 1983[37]	Richmond, Va	6	6 (100)
Daly et al, 1984[52]	London	9	7 (78)
Vignola et al, 1984[53]	Miami, Fla	6	5 (83)
Zee-Cheng et al, 1984[41]	St Louis	11	5 (45)
Dec et al, 1985[43]	Boston	9	4 (44)
Hosenpud et al, 1985[44]	Portland, Ore	6	0 (0)
Mortensen et al, 1985[54]	Copenhagen	12	8 (67)
Salvi et al, 1987[55]	Trieste	17	14 (82)
Total		112	66 (59)

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

Overall, 59% of patients improved (Table 4).* The natural history of untreated active myocarditis is unknown, however. It is of interest, in light of the recent finding of viral genomes in biopsy specimens showing myocarditis, that no investigator reported abrupt myocardial deterioration or dissemination of viral infection as a result of immunosuppression.

Randomized Trial

Because of the causal role of myocarditis in the development of dilated cardiomyopathy and the morbidity of inappropriate immunosuppression, a large randomized trial is necessary to ascertain the efficacy of immunosuppressive therapy in myocarditis and to determine whether myocardial biopsy is justified in patients with heart failure of unknown cause. The Myocarditis Treatment Trial, a National Heart, Lung, and Blood Institute-sponsored multicenter study, was developed to answer this question. Eligible patients have unexplained congestive heart failure (an ejection fraction below 0.45) without evidence of coronary artery disease and biopsy-proved "active" myocarditis, confirmed by a panel of pathologists. A total of 23 enrollment centers in the United States, Canada, Great Britain, and Japan, coordinated at the University of Utah, serve as entry points into the study. Patients are randomly assigned to one of two treatment limbs (Figure 2):

Limb 1. Standard conventional therapy for congestive heart failure

Limb 2. Standard conventional therapy for congestive heart failure plus the administration of cyclosporine and low doses of prednisone

In limb 2, cyclosporine was chosen as the primary immunosuppressive agent because it selectively blocks the production of interleukin-2 and has become the cornerstone of immunosuppressive treatment in human solid organ transplantation.[56] With increasing frequency, this agent has been applied to the study of autoimmune diseases such as diabetes mellitus,[57] myasthenia gravis,[58] and rheumatoid arthritis.[59]

*References 34, 36, 37, 41, 43, 44, 50-55.

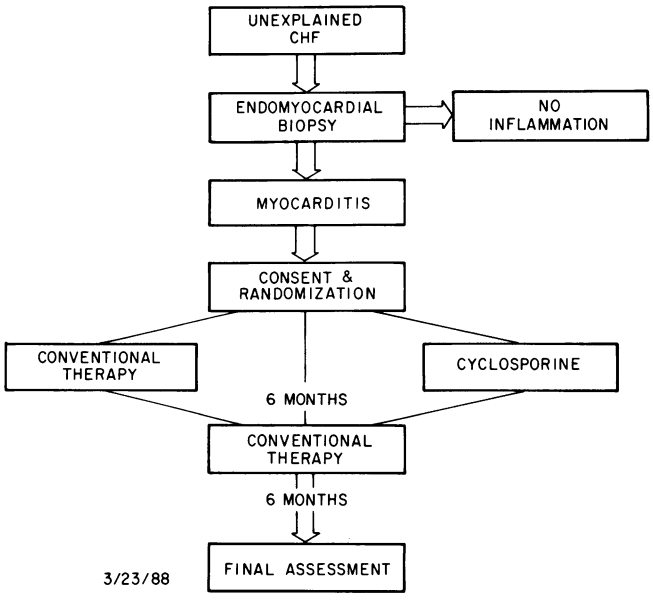

Figure 2.—The study design of the Myocarditis Treatment Trial is shown. CHF = congestive heart failure

Furthermore, it has theoretic advantages over azathioprine in that there is less predisposition to infection with opportunistic organisms and a lesser requirement for corticosteroids in the transplant population. After six months of randomized therapy, the immunosuppressive regimen is discontinued and patients are observed for six months before an end-point evaluation one year from the initial assignment. Primary end points are changes in the radionuclide ejection fraction and treadmill exercise performance.

If referral to a formal enrollment center is not possible, an abbreviated protocol is available for any patient with biopsy-proved myocarditis in any center in the United States where treadmill exercise testing and radionuclide ventriculography are available. When a patient has biopsy-proved myocarditis and is considered for a random assignment of therapy, the referring physician should contact one of us at (800) 441-5544 or (801) 581-7715. The pathology slides will be directed to a member of the pathology panel for diagnostic confirmation. After informed consent and documentation of a left ventricular ejection fraction of less than 0.45 by radionuclide ventriculography, the patient will be randomly assigned. If assigned to limb 2, the cyclosporine will be provided by the coordinating center. It is expected that this open-enrollment phase of the trial will accelerate patient acquisition and, hence, allow conclusions to be reached at an earlier time. This trial will be actively recruiting patients through 1990, and 200 patients will be randomly assigned by completion of the trial.

In addition to the clinical trial, this study involves assessing cell-mediated immune responses including characterizing the cells infiltrating the myocardial biopsy specimens, the subpopulations of cells in the peripheral blood, suppressor cell function, antibody-dependent cellular cytotoxicity, and natural killer cell activity. Humoral immune responses are measured by determining the presence of heart reactive antibody and specificity of the antibody for myocyte antigens such as myosin. In situ hybridization to detect enteroviral genomes is done on myocardial biopsy specimens with positive results and compared with a control group so that the role of the humoral and cellular arms of the immune system and the persistence of infective agents can be estimated. If the trial shows that active myocarditis responds to immunosuppressive therapy, it will be recommended that all patients fitting the profile of those who responded to therapy undergo myocardial biopsy and, if myocarditis is found, receive a trial of immunosuppression.

REFERENCES

1. Fuster V, Gersh BJ, Giuliani ER, et al: The natural history of idiopathic dilated cardiomyopathy. Am J Cardiol 1981; 47:525-531

2. O'Connell JB, Gunnar RM: Dilated-congestive cardiomyopathy: Prognostic features and therapy. Heart Transplant 1982; 2:7-17

3. Kaye MP: The Registry of the International Society for Heart Transplantation: Fourth official report—1987. J Heart Transplant 1987; 6:63-67

4. Corvisart JN: Essay on the Organic Diseases and Lesions of the Heart and Great Vessels. Philadelphia, Pa, Bradford, Read & A. Finley, 1812. Cited 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. Huber SA, Lodge PA: Coxsackievirus B-3 myocarditis—Identification of different pathogenic mechanisms in DBA/2 and BALB/c mice. Am J Pathol 1986; 122:284-291

7. Paque RE, Gauntt CJ, Nealon TJ, et al: Assessment of cell-mediated hypersensitivity against Coxsackie B3 viral-induced myocarditis utilizing hypertonic salt extracts of cardiac tissue. J Immunol 1978; 120:1672-1678

8. Huber SA, Lodge PA: Coxsackie virus B3 myocarditis in BALB/c mice—Evidence for autoimmunity to myocyte antigens. Am J Pathol 1984; 116:21-29

9. Neu N, Rose NR, Beisel KW, et al: Cardiac myosin induces myocarditis in genetically predisposed mice. J Immunol 1987; 139:3630-3636

10. Wilson FM, Miranda QR, Chason JL, et al: Residual pathologic changes following murine Coxsackie A and B myocarditis. Am J Pathol 1969; 55:253-265

11. Reyes MP, Ho KL, Smith E, et al: A mouse model of dilated-type cardiomyopathy due to Coxsackie virus B3. J Infect Dis 1981; 155:232-236

12. Sutton GC, Harding HB, Trueheart LRP, et al: Coxsackie B4 myocarditis in an adult: Successful isolation of virus from ventricular myocardium. Aerospace Med 1967; 38:66-69

13. Fletcher GF, Coleman MT, Feorino PM, et al: Viral antibodies in patients with primary myocardial disease. Am J Cardiol 1968; 21:6-10

14. Cambridge G, MacArthur CGC, Waterson AP, et al: Antibodies to Coxsackie B viruses in congestive cardiomyopathy. Br Heart J 1979; 41:692-696

15. Eggers HJ, Mertens TH: Viruses and myocardium: Notes of a virologist. Eur Heart J 1987; 8 (suppl J):129-133

16. Bowles NE, Richardson PJ, Olsen EGJ, et al: Detection of coxsackie-B-virus-specific RNA sequences in myocardial biopsy samples from patients with myocarditis and dilated cardiomyopathy. Lancet 1986; 1:1120-1123

17. Orinius E: The late cardiac prognosis after Coxsackie-B infection. Acta Med Scand 1968; 183:235-237

18. Levander-Lindgren MS: Studies in myocarditis—IV. Late prognosis. Cardiologia (Basel) 1965; 47:209-220

19. Bengtsson E, Lamberger B: Five-year follow-up study of cases suggestive of acute myocarditis. Am Heart J 1966; 72:751-763

20. Sainani GS, Krompotic E, Slodki SJ: Adult heart disease due to Coxsackie virus B infection. Medicine (Baltimore) 1968; 44:133-147

21. Bergström K, Erikson U, Nordbring F, et al: Acute non-rheumatic myopericarditis—A follow-up study. Scand J Infect Dis 1970; 2:7-16

22. Smith WG: Coxsackie B myopericarditis in adults. Am Heart J 1970; 80:34-46

23. Gerzēn P, Granath A, Holmgren B, et al: Acute myocarditis—A follow-up study. Br Heart J 1972; 34:575-583

24. Obeyesekere I, Hermon Y: Arbovirus heart disease: Myocarditis and cardiomyopathy following dengue and chikungunya fever—A follow-up study. Am Heart J 1973; 85:186-194

25. Hayakawa M, Inoh T, Yokota Y, et al: A long-term follow-up study of acute viral and idiopathic myocarditis. Jpn Circ J 1983; 47:1304-1309

26. Torp A: Incidence of congestive cardiomyopathy. Postgrad Med J 1978; 54:435-437

27. Quigley PJ, Richardson PJ, Meaney BT, et al: Long-term follow-up of acute myocarditis—Correlation of ventricular function and outcome. Eur Heart J 1987; 8 (suppl J):39-42

28. Sekiguchi M, Hiroe M, Hiramitsu S, et al: Natural history of viral idiopathic myocarditis—A clinical and endomyocardial biopsy follow-up, *In* Schultheiss HP (Ed): New Concepts in Viral Heart Disease. Heidelberg, W Germany, Springer-Verlag, 1988, pp 33-50

29. Fowles RE, Bieber CP, Stinson EB: Defective in vitro suppressor cell function in idiopathic congestive cardiomyopathy. Circulation 1979; 59:483-491

30. Eckstein R, Mempel W, Bolte HD: Reduced suppressor cell activity in congestive cardiomyopathy and in myocarditis. Circulation 1982; 65:1224-1229

31. O'Connell JB, Fowles RE, Robinson JA, et al: Clinical and pathologic findings of myocarditis in two families with dilated cardiomyopathy. Am Heart J 1984; 107:127-135

32. O'Connell JB, Costanzo-Nordin MR, Subramanian R, et al: Peripartum cardiomyopathy: Clinical, hemodynamic, histologic and prognostic characteristics. J Am Coll Cardiol 1986; 8:52-56

33. O'Connell JB, Robinson JA, Gunnar RM, et al: Clinical aspects of virus/immune myocarditis. Heart Vess 1985; suppl 1:102-106

34. Mason JW, Billingham ME, Ricci DR: Treatment of acute inflammatory myocarditis assisted by endomyocardial biopsy. Am J Cardiol 1980; 45:1037-1044

35. Nippoldt TB, Edwards WD, Holmes DR Jr, et al: Right ventricular endomyocardial biopsy: Clinicopathologic correlates in 100 consecutive patients. Mayo Clin Proc 1982; 57:407-481

36. Fenoglio JJ Jr, Ursell PC, Kellogg CF, et al: Diagnosis and classification of myocarditis by endomyocardial biopsy. N Engl J Med 1983; 308:12-18

37. Hess ML, Hastillo A, Moharty PK: Inflammatory myocarditis: Incidence and response T-lymphocyte depletion (Abstr). J Am Coll Cardiol 1983; 1:584

38. Unverferth DV, Fetters JK, Unverferth BJ, et al: Human myocardial histologic characteristics in congestive heart failure. Circulation 1983; 68:1194-1200

39. Strain JE, Grose RM, Hirsch CL, et al: Atypical presentations of myocarditis (Abstr). Circulation 1983; 68 (suppl III):III-27

40. Parillo JE, Aretz HT, Palacios IF, et al: The results of transvenous endomyocardial biopsy can frequently be used to diagnose myocardial diseases in patients with idiopathic heart failure—Endomyocardial biopsies in 100 consecutive patients revealed a substantial incidence of myocarditis. Circulation 1984; 69:93-101

41. Zee-Cheng CS, Tsai CC, Palmer DC, et al: High incidence of myocarditis by endomyocardial biopsy in patients with idiopathic congestive cardiomyopathy. J Am Coll Cardiol 1984; 3:63-70

42. O'Connell JB, Henkin RE, Robinson JA, et al: Gallium-67 imaging in patients with dilated cardiomyopathy and biopsy-proven myocarditis. Circulation 1984; 70:58-62

43. Dec GW, Palacios IF, Fallon JT, et al: Active myocarditis in the spectrum of acute dilated cardiomyopathies—Clinical features, histologic correlates, and clinical outcome. N Engl J Med 1985; 312:885-890

44. Hosenpud JD, McAnulty JH, Miles 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

45. Cassling RS, Linder J, Sears TD, et al: Quantitation of inflammation in biopsy specimens from idiopathically failing or irritable hearts: Experience in 80 pediatric and adult patients. Am Heart J 1985; 110:713-720

46. French WJ, Siegel RJ, Cohen AH, et al: Yield of endomyocardial biopsy in patients with biventricular failure—Comparison of patients with normal versus reduced left ventricular ejection fraction. Chest 1986; 90:181-184

47. Aretz HT, Billingham ME, Edwards WD, et al: Myocarditis: A histopathologic definition and classification. Am J Cardiovasc Pathol 1987; 1:3-14

48. Spielgelhelter DJ, Stovin TGI: An analysis of repeated biopsies following cardiac transplantation. Stat Med 1983; 2:33-40

49. Yasuda T, Palacios IF, Dec GW, et al: Indium-111 monoclonal antimyosin imaging in the diagnosis of acute myocarditis. Circulation 1987; 76:306-311

50. Sekiguchi M, Hiroe M, Take M, et al: Clinical and histopathological profile of sarcoidosis of the heart and acute idiopathic myocarditis—Concepts through a study employing endomyocardial biopsy: II—Myocarditis. Jpn Circ J 1980; 44:264-273

51. Edwards WD, Holmes DR Jr, Reeder GS: Diagnosis of active lymphocytic myocarditis by endomyocardial biopsy—Quantitative criteria for light microscopy. Mayo Clin Proc 1982; 57:419-425

52. Daly K, Richardson PJ, Olsen EGJ, et al: Acute myocarditis—Role of histologic and virological examination in the diagnosis and assessment of immunosuppressive treatment. Br Heart J 1984; 51:30-35

53. Vignola PA, Aonuma K, Swaye PS, et al: Lymphocytic myocarditis presenting as unexplained ventricular arrhythmias: Diagnosis with endomyocardial biopsy and response to immunosuppression. J Am Coll Cardiol 1984; 4:812-819

54. Mortensen SA, Baandrup U, Buch J, et al: Immunosuppressive therapy of biopsy-proven myocarditis: Experiences with corticosteroids and cyclosporine. Int J Immunotherapy 1985; 1:35-45

55. Salvi A, Hrovatin E, Dreas L, et al: Changes in histology and left ventricular function during immunosuppressive treatment in active myocarditis. Eur Heart J 1987; 8 (suppl J):267-269

56. Kahan BD: Immunosuppressive therapy with cyclosporine for cardiac transplantation. Circulation 1987; 75:40-56

57. Bach JF: Cyclosporine in type I diabetes: Rationale, expected benefits and potential limitations. Transplant Proc 1986; 18:1537-1539

58. Tindall RSA, Rollins JA, Phillips JT, et al: Preliminary results of a double-blind, randomized, placebo-controlled trial of cyclosporine in myasthenia gravis. N Engl J Med 1987; 316:719-724

59. Berg KJ, Forr O, Bjerkhoel F, et al: Side effects of cyclosporin A treatment in patients with rheumatoid arthritis. Kidney Int 1986; 29:1180-1187