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Editorial Comment

The Safety and Utility of Endomyocardial Biopsy in Infants, Children and Adolescents*

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Biopsy of the kidney, liver, bone marrow and other organs is routinely performed in clinical medicine. Endomyocardial biopsy also has now become a routine diagnostic procedure in many medical centers around the world. In 1962, the Japanese team of Sakakibara and Konno (1) introduced a bioptome for a transvenous approach to the heart. By 1970, the efficacy of this type of bioptome had been conclusively demonstrated and accepted in the Western world. There have been many modifications of the original bioptome, as well as variations in technique for obtaining myocardial biopsies, and the indications for endomyocardial biopsy have increased. More recently, several of the bioptomes have been modified to include a pediatric bioptome, which can be used for very young children including neonates.

In this issue of the Journal, Yoshizato et al. (2) present an updated review of the safety and utility of endomyocardial biopsy in infants and children. Their study is of interest because there are still relatively few reports regarding the complications and results of endomyocardial biopsy in children. Although their study includes children aged 2 months to 20 years, the mean age of their 53 patients was 13 years; 25% of the patients were ≤10 years old. The importance of their study, which is primarily a nontransplant diagnostic endomyocardial biopsy study in children, is that it is also applicable to the burgeoning heart transplantation setting. At present, cardiac transplantation management relies heavily, and almost exclusively on the morphologic index obtained by endomyocardial biopsy for the diagnosis of acute rejection.

From International Society of Heart Transplantation records (3), the age group for cardiac transplantation and combined heart-lung transplantation has been extended to include neonates and very young children. Heart transplantation in the youngest recipients was performed at birth, and combined heart-lung transplantation has been performed in children 3 months old. Between 1984 and 1988, >65 children <1 month old received a cardiac transplant, as did a total of 233 children <10 years old received a transplant (Fig. 1).

The present study. With the exponential rise in cardiac transplantation in this country, it is clear that more and more children will require endomyocardial biopsy. The study by Yoshizato et al. (2) adds to our knowledge of such biopsies by describing the results of 66 procedures in 53 children. It is encouraging to note that the endomyocardial biopsies in this group were either diagnostic or confirmatory in 67% to 96%. It is also encouraging that 96% of the endomyocardial biopsies were successful, and that a mean of five biopsy specimens was obtained in each biopsy procedure, a number that not only is adequate for diagnosis, but also is a satisfactory number to minimize the sampling error inherent in endomyocardial biopsy.

The authors (2) suggest that in two cases the biopsies were not helpful, because "normal" tissue was obtained. One can take the view that these normal biopsies are indeed very helpful, because they rule out conditions that cause hypertrophy and fibrosis or other conditions that are diffuse in nature, such as hemochromatosis or metabolic storage diseases. A related point is that attitude in examining small pieces of myocardium is important. For example, one can report nonspecific hypertrophy or one can observe that hypertrophy in a small child confirms or "is consistent with" the clinical suspicion of cardiomyopathy, which is the more useful approach.

In discussing cardiomyopathy, the authors have stated that "in most cases, biopsy tissues demonstrate myocyte hypertrophy and interstitial fibrosis, thereby confirming a diagnosis of cardiomyopathy; but these findings are nonspecific and do not provide information concerning possible causes of the disorder." However, no special studies were performed and the use of electron microscopy was not addressed. For example, in some cases of familial cardiomyopathy (4), mitochondrial abnormalities may be seen, and today it is also possible to study these small biopsy specimens with new techniques, such as polymerase chain reaction.

Diagnosis of myocarditis. The report by Yoshizato et al. (2) raises the question of myocarditis and, once again, confirms the poor correlation between the clinical and biopsy diagnoses of acute myocarditis in infants, children and

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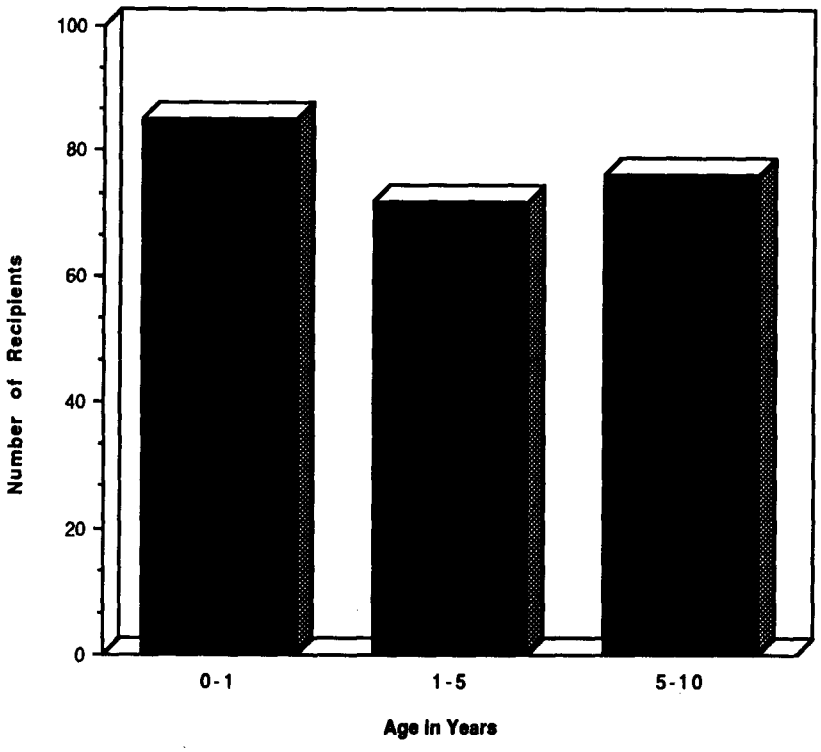

Figure 1. Age distribution in 233 child cardiac recipients (1984 to 1988). (Modified from the International Society of Heart Transplantation Registry.)

adolescents. This finding supports the emerging awareness that the clinical diagnosis of acute myocarditis is often not confirmed morphologically. This discrepancy is not necessarily a sampling error of the biopsy, but rather an indication that there is indeed no acute myocarditis, and that it is being mimicked clinically by cardiomyopathy or other conditions. This possibility is borne out by the large number of transplant patients with suspected acute myocarditis whose explanted heart manifests the pathologic features of end-stage cardiomyopathy of the dilated type. Sometimes there are residual foci of lymphocytes, and there have been many published discussions (5,6) as to the nature of these lymphocytes; although they may be residual from a previous episode of acute myocarditis, they probably do not represent acute myocarditis at this stage. This is particularly true in children, because a background of hypertrophy and fibrosis would be totally inconsistent with acute myocarditis and, by the time the hypertrophy and fibrosis are evident, the child already has developed a cardiomyopathy, even though residual lymphocytes may be seen. Children dying of acute myocarditis have florid interstitial infiltrates with myocyte necrosis and usually no background hypertrophy and fibrosis. One would expect children presenting with heart failure to have a florid, diffuse, rather than focal, inflammatory infiltrate (although focal infiltrates could result in arrhythmias).

Complications of endomyocardial biopsy. The question of the morbidity of endomyocardial biopsy in children is important. Although the need for general anesthesia is not addressed by Yoshizato et al. (2), it should be remembered that infants and young children require general anesthesia to obviate the possibility that air embolus might occur while they are crying during the procedure. Anesthesia is an extra hazard that is not necessary in older children or adults. Serious complications in children are rare in other reported series. At Stanford, there have been no cardiac perforations in 200 cardiac biopsies in children (unpublished data). In the report by Yoshizato et al. (2), three cardiac perforations were recorded, although in each case the outcome was good. It is interesting to speculate whether this higher rate of perforation might be due to the femoral approach used exclusively by their group or to the type of bioptome used. The more direct approach through the right internal jugular vein with a size 5F or 6F bioptome might be safer in very young children. This question still needs to be answered. It should also be stated that these invasive studies should be performed only by skilled and experienced invasive cardiologists or surgeons.

Conclusions. Endomyocardial biopsy has made possible the earliest morphologic detection of cardiac disease in the living patient, has allowed the evolution of the disease to be followed and has documented its morphologic reversal after a course of treatment. With the application of new techniques of immunohistochemistry, ultrastructural changes, gene rearrangement techniques and cardiac receptor studies to the diagnosis and treatment of cardiovascular disease, the potential role of endomyocardial biopsy is greater. These advances can now be extended to the

pediatric group of patients in whom endomyocardial biopsy is possible.

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