Fig. 2. Roentgenogram of the chest 30 days after repair. A residual hematoma of the right upper lobe and good expansion of the right lower lobe can be seen.

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HLA ANTIBODIES SPECIFIC FOR CRYOPRESERVED HEART VALVE "HOMOGRAFTS" IN CHILDREN

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For more than 30 years, human heart valves have been used as grafts for replacement of diseased aortic and pulmonary valves. These heart valve allografts, tradition-

ally referred to as "homografts," were long assumed to be immunologically inert and were supposed not to be affected by rejection, in contrast to organ transplants. However, in children, degeneration of the heart valve allografts is frequently observed.¹ Findings in clinical^{2,3} and experimental⁴ studies suggested that this degeneration might be caused by an immune response. Recently, Smith and colleagues⁵ from the Harefield Hospital, United Kingdom, found donor HLA-specific antibodies in adults after implantation of fresh or antibiotic-sterilized aortic valve allografts. This demonstrated that human heart valve allografts can induce immune responses in patients.

Most cardiac centers do not have fresh heart valve allografts available and use cryopreserved valves instead, which have been shown to become less immunogenic during the cryopreservation procedure.³ Therefore we investigated whether cryopreserved heart valve allografts induced donor-specific HLA antibodies in children.

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Table I. *Specificity and isotype of HLA antibodies in eight children with cryopreserved heart valve allografts*

Serum sample*	Age†	Diagnosis	Type of valve allograft	HLA antigens of valve donor	HLA antibodies and isotype	Red blood cells‡
2 Wk	1	Pulmonary valve atresia	Pulmonary	Not determined	B17; IgM	4
5 Mo	1	Pulmonary valve atresia	Aortic	A1, A2, B18, B37	A1; IgG	11
1 Yr	11	Tetralogy of Fallot	Aortic	Not determined	No	3
3 Yr	0	Truncus arteriosus	Aortic	First: A1, A2, B37, B39	No	0
3.5 Yr§				Second: A2, A24, B18, B35		
4 Yr	17	Pulmonary valve stenosis	Pulmonary	A24, A32(A19), B44, B61	A10, A19; IgG	14
4.5 Yr	4	Pulmonary valve insufficiency	Aortic	Not determined	No	5
5 Yr	1	Tetralogy of Fallot	Aortic	A24, B51(B5), B49	B5, B49; IgG	8
5 Yr	6	Aortic valve stenosis	Aortic	First: A1, A24, B8, B39	No	3
6 Yr§				Second: Not determined		

*Time after operation.

†Age in years at time of operation.

‡Units of unfiltered red blood cell concentrates received perioperatively.

§Patient underwent operation twice.

Table II. *Specificity of HLA antibodies in one patient and HLA antigens of heart valve donor and blood donors*

HLA specificity/antigens	
HLA antibodies	B5, B49
Valve donor	A24, B51(B5), B49
Blood donor 1	A2, B7, B62
Blood donor 2	A2, A3, B7
Blood donor 3	A29, A32, B44
Blood donor 4	A1, A2, B62, B37
Blood donor 5	A2, A30/A31, B44, B27
Blood donor 6	A1, A24, B7, B8
Blood donor 7	A3, A30/31, B13, B35
Blood donor 8	Not determined

Eight children who underwent operation for congenital heart defects (Table I) were studied between 2 weeks and 5 years after implantation of a cryopreserved heart valve allograft. The age of the children at the time of operation ranged from 1 month to 17 years; two of the children had undergone operation twice; all but one of the children received unfiltered red blood cell concentrates (Table I). In a study protocol approved by the Medical Ethical Committee of our institution, the patients (and parents) allowed collection of a single blood sample for analysis of HLA antibodies; no permission was obtained for HLA typing in these patients.

For the detection of cytotoxic anti-HLA class I antibodies and for the crossmatches, the standard National Institutes of Health microlymphocytotoxicity technique and a more sensitive assay that used longer incubation times were used. The sera were screened against peripheral blood lymphocytes of a panel of 40 different HLA-typed healthy volunteers. Pretreatment of the sera with dithiothreitol was used to differentiate between immunoglobulin (Ig) G and IgM antibodies.

Cytotoxic HLA antibodies were detected in the serum of four of the eight children. In three children HLA antibodies of the IgG isotype were directed specifically

against HLA antigens of the allograft donor; the donor specificity of the IgM HLA antibodies detected in the fourth patient could not be confirmed because the donor HLA typing was not available.

In one patient, with HLA antibodies specific for the relatively rare HLA-B5 and -B49 antigens, analysis was done in detail, to exclude the possibility that the HLA antibodies were induced by blood transfusions. All but one of the blood donors were retrospectively typed for HLA antigens. None of the blood donors had the B5 or B49 antigens (Table II) and the crossmatches between the serum of the patient and lymphocytes of the blood donors were all negative. One blood donor was not available for HLA typing but it is unlikely that this single donor had HLA antigens corresponding with the specificities of the HLA antibodies.

This report demonstrates that in children cryopreserved heart valve allografts can induce donor-specific, cytotoxic HLA antibody responses. Children have high humoral anti-HLA responsiveness,⁶ and they also frequently show degeneration of implanted heart valve allograft.¹ If we accept the concept that this degeneration is immune mediated, the obvious consequence for clinical treatment of the children would be to prevent the immune response against the heart valve allograft. One way to achieve this could be treatment of patients with immunosuppressive drugs as was shown effective in rats.⁷ For children this treatment is not appealing, because of the side effects of immunosuppression.

Another way to prevent immune responses against valve allografts is prospective selection of an HLA-matched valve for each patient. Ideally the allografts should be matched for both HLA class I and II antigens. Class I matching has been shown to reduce rejection in high-risk corneal transplantation⁸ and class II matching reduced in vitro the stimulation of lymphocytes by heart valve tissue.³ The major obstacle to achieving adequate HLA matching of heart valve allografts, next to size matching, is that it would restrict the availability of suitable valve allografts for individual patients. In addition, the effect of prospective matching would only be of

benefit for patients with an increased risk for degeneration of the valves. At present it is impossible to assess prospectively which patients are at risk for immune-mediated valve degeneration. However, children listed for retransplantation for reasons other than technical failure and children with preformed HLA antibodies are likely candidates. We recommend that for these patients at "high risk" a crossmatch-negative, HLA-matched heart valve allograft be selected.

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MULTIPLE EPISODES OF THROMBOSIS WITH BIVENTRICULAR SUPPORT DEVICES WITH INADEQUATE ANTICOAGULATION AND EVIDENCE OF ACCELERATED INTRAVASCULAR COAGULATION

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Ventricular assist devices (VADs) may induce complex hemostatic abnormalities mediated by excessive activation of platelets, coagulation, and fibrinolysis with resulting consumption of platelets and labile coagulation factors and sometimes associated with thrombosis.¹⁻³ We describe the case of a teenaged boy with

dilated cardiomyopathy whose course was initially complicated by excessive bleeding. He subsequently had multiple episodes of thrombosis of biventricular assist devices (BVADs) that were associated with accelerated intravascular coagulation temporally related to suboptimal warfarin anticoagulation.

A 15-year-old boy with Becker's muscular dystrophy was admitted for treatment of progressive congestive heart failure. Transthoracic echocardiography revealed dilated cardiomyopathy with severely reduced ejection fraction and a right ventricular mural thrombus. Over a 3-week period after admission, he began having increasingly severe symptoms of congestive heart failure with respiratory distress and profound hypotension. The symptoms were unresponsive to aggressive medical management with inotropic support, diuresis, afterload reduction, and intraaortic balloon counterpulsation. After the development of cardiogenic shock, ABIOMED BVADs (ABIOMED Cardiovascular, Inc., Danvers, Mass.) were implanted as a bridge to transplantation (day 1). The patient was given a continuous infusion of heparin at a rate of 1500 to 2200 U/hr to maintain the celite activated clotting time between 180 and 200 seconds. While he was

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