

## Cardiac Transplantation with Cyclosporin A and Prednisone

BARTLEY P. GRIFFITH, M.D., ROBERT L. HARDESTY, M.D., G. MICHAEL DEEB, M.D.,  
THOMAS E. STARZL, M.D., HENRY T. BAHNSON, M.D.

Influenced by continuing improvement in results from Stanford, cardiac transplantation was resumed at the University Health Center of Pittsburgh in June 1980. Cyclosporin A (CyA) became available to the authors early in 1981. This report describes the preliminary experience with 21 patients who were treated between March 1981 and April 10, 1982 with cyclosporin A and low-dose steroids. Ages ranged from eight to 53 years, median 46 years. Median age of ten patients disabled because of idiopathic myocardiopathy was 33 years; it was 45 years in the 11 suffering from ischemic heart disease. Sixteen of the 21 patients survived. Eleven have survived for three months, of which six have survived for six months, giving a cumulative survival of 74 and 66%, respectively. Four died perioperatively; one died at six weeks and one at four months. Hyperacute rejection resulted in one death at 12 hours even though the warm and cold lymphocytotoxic crossmatch for T and B cells was negative as evaluated by trypan blue. The two late deaths were related to infection. No late death has occurred because of rejection, and a unique feature is that three recipients with a lymphocytotoxic mismatch did not develop hyperacute rejection. The number of infectious episodes and nonviral infections appears to be less than that associated with the use of azathioprine and larger doses of steroids. Cyclosporin A (5–10 mg/kg/d) and low-dose prednisone (rapidly tapered in seven days from 200 mg to 15–20 mg/d) is effective in preventing early morbid rejection of the transplanted heart.

**I**NFLUENCED BY THE continuing improvement in results reported from Stanford,<sup>1,2</sup> the authors resumed cardiac transplantation in June 1980. Cyclosporin A (CyA) became available to the authors in Pittsburgh early in 1981. At that time there was evidence that significantly better results could be obtained with CyA than with azathioprine (Aza) for transplantation of kidneys and livers.<sup>3-5</sup> A randomized trial of CyA vs. conventional treatment with Aza for renal transplantation was underway at the University Health Center of Pittsburgh, and CyA was the agent used routinely with hepatic transplantation. With this background CyA with steroids, but without other immunosuppressive drugs, was adopted as the routine immunosuppressive agent. This report describes preliminary ex-

*From the Department of Surgery, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania*

perience with 21 patients who were treated between March 1981 and April 10, 1982 with Cyclosporin A and steroids.

### Patient Selection

Most of the 21 patients selected for transplantation met the criteria described by Baumgartner et al.<sup>2</sup> All were NYHA Class IV. Ages ranged from eight to 53 years, median 46 years. Median age of ten patients disabled because of idiopathic cardiomyopathy was 33 years; it was 45 years in the 11 suffering from ischemic heart disease. Seven patients were receiving inotropic drugs intravenously on admission to the hospital, ventilation was assisted in three, and two were on balloon assist devices. Three patients could be weaned from the drip or assist device before operation.

ABO blood type was compatible in all cases. Compatibility of donor lymphocytes with recipient serum was desired and was evaluated in all cases. In three cases in which the donor heart was procured from a distant city, a positive T and B, warm and cold, mismatch against donor lymphocytes was first known during implantation of the donor heart. More recently serum of the recipient has been sent to the location of the donor, and compatibility determined before removal of the recipient's heart.

### Immunosuppression

Cyclosporin A has been given orally just before operation. An intravenous preparation has been available since December 1981, but in some hemodynamically unstable patients, this has caused hypotension, and it is now used only in case of great urgency. Initially the dosage schedule that had been developed with renal transplantation of 17.5 mg/kg/d was used.<sup>4</sup> Because of oliguria soon after operation, which did not seem related to the operation, the dose was reduced, and the usual dose at present is 10 mg/kg/d. When given in-

Presented at the Annual Meeting of the American Surgical Association, Boston, Massachusetts, April 21–23, 1982.

Reprint requests: Bartley P. Griffith, M.D., Department of Surgery, University of Pittsburgh School of Medicine, 1088 Scaife Hall, Pittsburgh, Pennsylvania 15261.

travenously, 40% of this dose was used. Because of elevation of serum creatinine in five patients, bilirubin in two, and both in two additional patients, the CyA dose was reduced from 10 mg/kg/d and averaged 8 mg/kg/d (range 4–10 mg/kg/d) in the 13 patients discharged from the hospital.

Previous experience with steroid drugs and CyA suggested that large initial doses could be rapidly tapered to low maintenance levels, thereby avoiding some of the morbid side effects of steroids.<sup>4,5</sup> The authors' practice reflects aiming for this goal. One g of methylprednisolone has been given as the aorta was released and circulation restored to the donor heart during transplantation. Prednisone, 200 mg/d, in two divided doses was started after operation, and the daily dose was reduced by 20 mg each day to a maintenance level of 15 to 20 mg daily. If oral medication was not possible, an equivalent dose of methylprednisolone was given intravenously. Because of its short duration of action, hydrocortisone, 1 g intravenously, was used to combat rejection, usually without alteration of the course of prednisone. The number and frequency of pulses was varied depending upon the degree of rejection as determined by clinical signs, or more commonly, by endomyocardial biopsy (Table 1).

In case of severe acute rejection, three daily doses of hydrocortisone were given. For less severe rejection, the pulsed doses were given at three-, five-, or seven-day intervals. The last regimen, that is, three doses of hydrocortisone at weekly intervals, was used for outpatients with mild histologic evidence of rejection.

In one instance of severe, acute rejection, in addition to three daily doses of hydrocortisone, the daily oral dose of prednisone was restored to 200 mg and subsequently reduced over the following five days to the original maintenance level (Fig. 1).

The amount of drugs was adjusted to the surface area of the eight-year-old patient. Antithymocyte globulin has not been used in this series of patients.

#### Operative Technique and Donor Procurement

In all cases orthotopic cardiac transplantation was performed utilizing the techniques described by Lower and Shumway.<sup>1,6</sup> The method of preservation of the donor heart varied with respect to the use of cardioplegic solution. All grafts were immediately immersed and transported in a 4 C crystalloid solution. Most donor hearts were perfused with 650 to 1000 ml of Stanford cardioplegic solution (4 C) before cardiectomy, and recently, additional doses of blood cardioplegia have been given during implantation. The latter method has been associated with a lesser need for postoperative inotropic support.

TABLE 1. Immunosuppression Protocol for CyA and Low-dose Prednisone

IMMUNE SUPPRESSION		
<b>CYCLOSPORIN A</b>		
MAXIMAL DOSE TOLERATED (Renal-Hepatic) 5-10-17.5 mg/kg/d		
<b>STEROIDS</b>		
INITIAL	Methylprednisolone	1 gm
MAINTENANCE	Prednisone	200 mg/d ↓ 10 d 15-20 mg/d
PULSE	Hydrocortisone	1 gm

Donor referrals have been to the Transplant Organ Procurement Foundation of the University of Pittsburgh. Thirteen patients received donor hearts procured from a distant city and the median transport time was 112 minutes (range 75–131 minutes). To this was added the median 61 minutes of implantation from arrival of the heart to release of the aortic clamp.

#### Results

##### Mortality

Sixteen of the 21 patients survived during the period of study. Eleven have survived for three months, of which six have survived for six months, giving a cumulative survival of 74 and 66%, respectively (Fig. 2). Four patients died perioperatively; one died at six weeks and one at four months.

Hyperacute rejection resulted in one death at 12

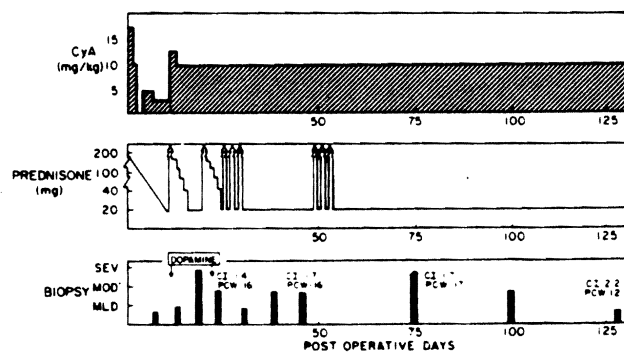


FIG. 1. Immunotherapy plus hemodynamic and biopsy findings in one patient with early severe rejection. CyA was discontinued perioperatively because of renal toxicity.

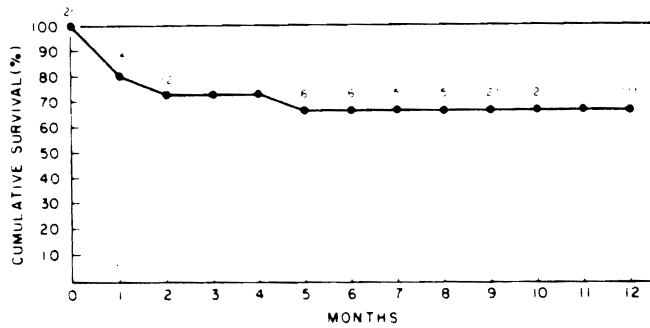


FIG. 2. Actuarial survival curve for all patients treated from March 1981 to April 1982.

hours even though the warm and cold lymphocytotoxic crossmatch for T and B cells was negative as evaluated by trypan blue. This patient had had a PRA (percentage reactive antibodies) that varied from 30 to 100% while awaiting transplantation. Myocytolysis, arterioles containing IgM and fibrinogen, and sludging of red blood cells in the capillaries was interpreted as hyperacute rejection. Two patients died of multiple complications related to severe cerebral infarctions. One of these had nearly recovered from a cerebral embolus that had occurred one week before transplantation. Following the operation, he never regained normal cerebral function. The second had been supported with diastolic augmentation and large amounts of inotropic drugs for two weeks before transplantation. At operation there was thrombus attached to the ascending aortic wall. An uneventful convalescence was interrupted by a cerebral embolus that resulted in a neurologically related death. Extensive thrombus was present in the distal ascending

aorta and beyond. In the fourth case, a small donor heart never generated an adequate cardiac output when transplanted into an adult with pulmonary hypertension.

The two late deaths were related to infection, bacteroides peritonitis of an inexplicable source, and cytomegalic pneumonia with an associated enterobacter-mediastinal abscess.

### Rejection

Endomyocardial biopsies obtained with the Caves-Schultz Stanford bioprobe provided a morphologic index of rejection as defined by Billingham.<sup>7</sup> Mild and moderate histologic evidence of rejection is common during the initial six weeks following transplantation (Fig. 3). When CyA was reduced to less than 5 mg/kg/d, two patients had severe histologic evidence of rejection, one of which was associated with a moderate fall in blood pressure and one with severe congestive heart failure and hypotension (Fig. 1). These episodes resolved over two weeks following increases in the CyA dose and pulse therapy with hydrocortisone. At four weeks and again at six months after transplantation, severe histologic rejection was found in another patient. The early episode was not accompanied by clinical signs and occurred with a CyA dose of 17.5 mg/kg/d. The late rejection was associated with moderate congestive heart failure with a dose of CyA of 6 mg/kg/d and prednisone of 20 mg/d. Each of these episodes was reversed through the use of pulse therapy.

Two of three recipients survived despite having lymphocytotoxic antibodies to the donor's lymphocytes by two-color immunofluorescence technique with ethidium bromide. Within the first six weeks, both had moderate histologic rejection and mild cardiac failure. The first died at six weeks of infection after having received more pulse therapy, due to the authors' special concern, than would have been administered had the mismatch not been present. The second, alive two months later, was treated without consideration of the mismatch and on the basis of biopsies. At two weeks, moderate deposition of IgM in the arterioles was correlated with moderate histologic rejection. Both findings resolved at two months—no IgM, mild histologic rejection.<sup>8</sup>

The third patient who had lymphocytotoxic antibodies to the donor's lymphocytes died 30 hours after operation of low cardiac output (the fourth case referred to previously under mortality). This recipient had received a small donor heart and had moderately elevated pulmonary vascular resistance preoperatively (7 Wood units). The heart had minimal deposition of IgM and fibrinogen without red cell sludging, and so the findings were inconsistent with hyperacute rejection (Table 2).

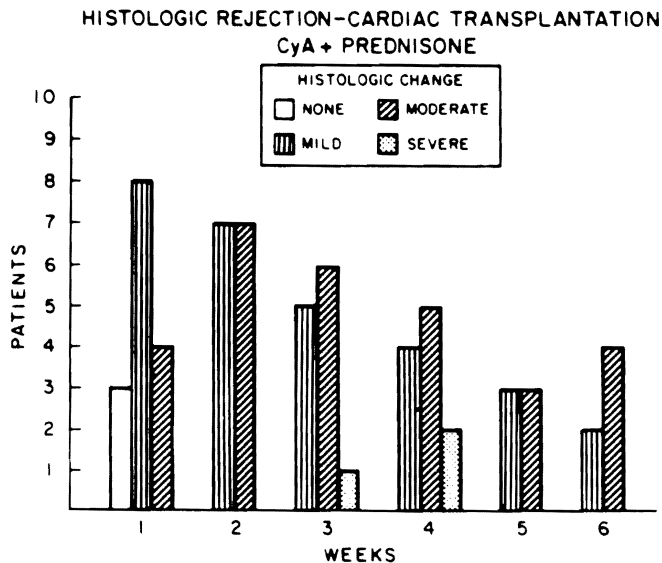


FIG. 3. Grades of histologic changes noted on endomyocardial biopsy specimens in 15 patients.

Biopsies of all recipients treated with CyA and low-dose prednisone have a scattered, focal, fine, interstitial fibrosis that becomes evident within two weeks whether or not acute rejection has occurred (Fig. 4). Scattered, focal interstitial mononuclear cells are common and do not portend rejection. A moderate amount of myocardial fibrosis has been evident following episodes of rejection.

### Infection

Infectious episodes have been monitored by the Division of Infectious Diseases. In addition to the first 14 cardiac recipients, this experience includes information on patients receiving a primary renal transplant who were randomized to treatment with Aza, 11 patients, or CyA, 15 patients, and 18 patients receiving a second renal transplant and treated with CyA<sup>9</sup> (Table 3).

The fraction of patients developing one or more infections was highest in the primary renal Aza group (91%) and less in the CyA renal (67%) and cardiac (70%) groups. These differences are not statistically significant. The mean number of infectious episodes per patient was also highest in the primary renal Aza group

TABLE 2. Summary of Findings of Biopsy and Autopsy Specimens in Four Patients with Positive Warm T and B Cell Crossmatches

LYMPHOCYTOTOXIC CROSSMATCH				
	IgM	Fib	SLUDGE	OUTCOME
POSITIVE	+/-	+/-	-	LIVED 6WK
POSITIVE	+/-	-	-	ALIVE 2MO
NEGATIVE*	++	++++	++++	DEAD 12HR
POSITIVE	+	+	-	DEAD 30HR

(2.4/patient). Nonviral infections were highest in the primary renal Aza group (1.5/patient) compared with the CyA renal (0.5/patient) and cardiac (0.9/patient) groups. The differences in infectious episodes and nonviral infections per patient are all significant ( $p < 0.05$ ).

Twenty infectious episodes occurred in 11 of the 14 cardiac patients on CyA. Eight pulmonary infections in six patients was the leading site, compared with three cutaneous in three, one urinary tract in one, five gas-

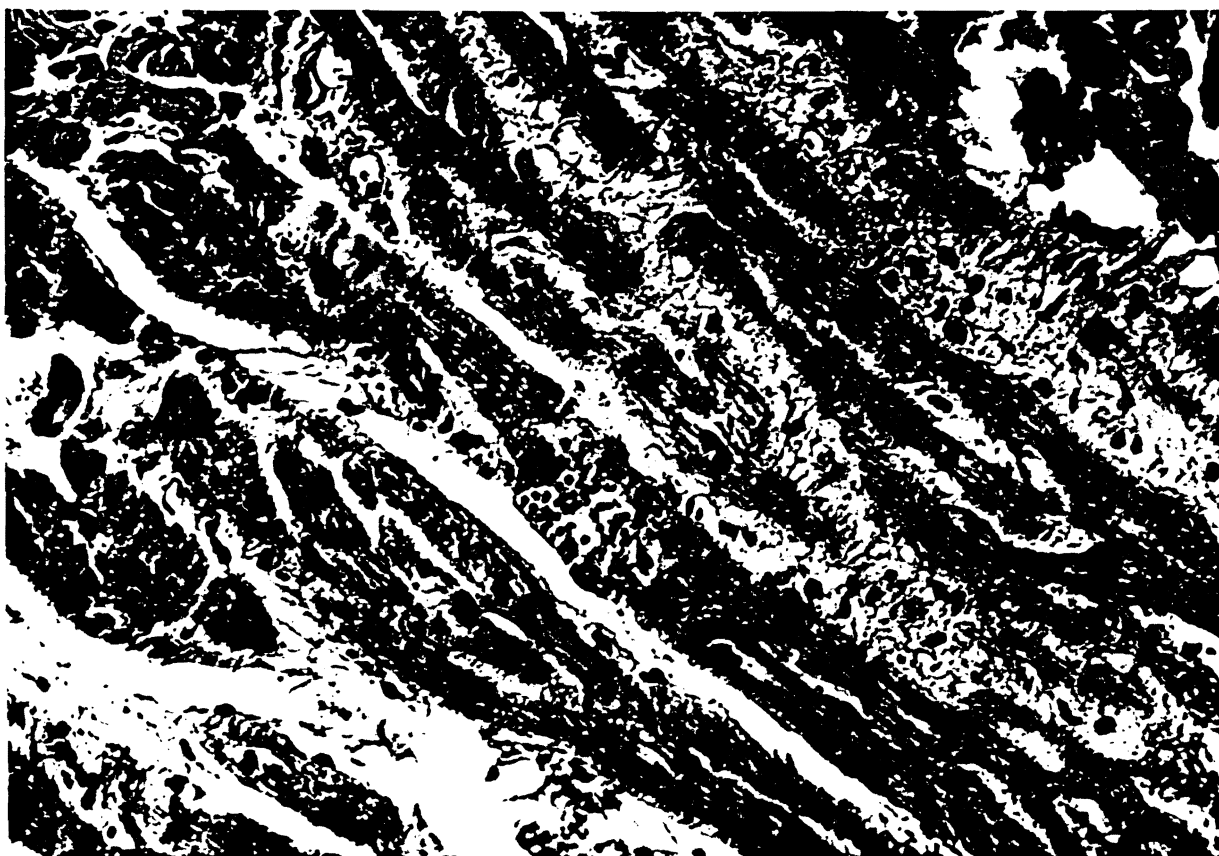


FIG. 4. Endomyocardial biopsy specimen demonstrating interstitial fibrosis (hematoxylin-eosin,  $\times 170$ ).

TABLE 3. Infectious Episodes Noted in Randomized Aza vs. CyA Renal Transplant Trial and in 14 Patients Receiving CyA Following Cardiac Transplantation

INFECTIOUS EPISODES			
	AZA	CyA	CyA
	RENAL	RENAL	CARDIAC
INFECTED/TOTAL	91%	67%	70%
NUMBER/PATIENT	2/4	0/9	1/4
NON-VIRAL/PATIENT	1/5	0/5	0/9
	n=11	n=33	n=14

trointestinal-peritoneal in four, and three other sites in two patients.

Twenty-one isolates in 11 patients included five gram-negative aerobes in five patients and four gram-positive organisms in three. Among the latter, there was one staphylococcus isolate in one patient, and 13 nonstaphylococcus organisms in 11. One fungal (*Aspergillus*) isolate occurred in one patient.

#### CyA Adverse Reactions

Diastolic hypertension has been present in 11 of 13 patients discharged from the hospital and tends to begin within the first postoperative week. It has developed irrespective of preoperative hypertension or measurable postoperative CyA renal toxicity. The observed hypertension has been difficult to control with diuretics and peripheral vasodilators. While studies are incomplete, the hypertension appears atypical in that the usual sleep related fall in diastolic pressure is not observed.

Hirsutism has occurred in all surviving patients and has been a cosmetic concern in the two adult female recipients. A fine tremor of the upper extremities and nasal congestion have been transient. Hyperplasia of the gums has occurred rarely, is dose related, and considered to be a manifestation of overdosage. A number of patients have been troubled after operation by gastrointestinal ileus resulting in abdominal distension which has required nasogastric drainage and cathartics.

#### Discussion

Following cardiac transplantation, immunosuppression is effective with CyA (5–10 mg/kg/d) and low-dose prednisone (rapidly tapered in seven days from 200 mg to 15–20 mg/d). Endomyocardial biopsy has been the primary index of rejection used to manage immunosuppression. Neither electrocardiographic voltage (summation of leads I, II, III, V<sub>1</sub> and V<sub>6</sub>) nor arrhyth-

mia has been reliably predictive of rejection. In the first six weeks, mild to moderate histologic rejection is common, but it usually is not associated with functional impairment of the graft or recipient. Pulse therapy with hydrocortisone alone is effective in reversing rejection. The single death attributed to rejection, which was hyperacute, occurred in a patient who matched on lymphocytotoxic testing by trypan blue. This test may be inadequately sensitive because on another occasion trypan blue failed to detect lymphocytotoxicity that was evident by two-color immunofluorescence with ethidium bromide. Especially in the presence of a high PRA, the latter technique should be used. A unique feature of this series is that three recipients with a lymphocytotoxic mismatch did not develop hyperacute rejection.

Two patients have died of infection, one at six weeks, and one at four months. Although the series is small and we have not had sufficient experience with cardiac transplants treated with Aza for a meaningful comparison from our own experience, experience with other organs at this institution has shown a lesser incidence of bacterial infection than that which occurred with Aza and steroids. The fraction of patients developing one or more infections, the mean number of infectious episodes per patient, and the mean number of nonviral infections is less than in patients who are treated with Aza. No predisposition for staphylococcal or fungal isolates is evident.

Factors related to selection of recipients and donors caused as many deaths, all perioperative, as did rejection and infection together. The two patients dying of neurologically-related causes would now not be transplanted; a small heart would now not be used for a large recipient, especially one with high pulmonary vascular resistance. None of these deaths reflects on CyA and low-dose prednisone as the immunosuppressive agent.

Preoperative use of CyA in amounts of 17.5 mg/kg is associated with an inordinately high incidence of postoperative oliguria whereas 10 mg/kg is less so, and the latter is currently the authors' loading dose. Renal toxicity mandates frequent monitoring and readjustment of maintenance doses, especially in the first several days after operation. Special caution is necessary should the amount be less than 5 mg/kg/d, and, should it be necessary to discontinue CyA for longer than 24 hours, Aza should be used temporarily. It is always possible to resume the use of CyA at a dose that is therapeutic and yet not toxic.

Hepatic toxicity does occur but is much less common than renal toxicity. It infrequently necessitates manipulation of the dose and never discontinuance of CyA for cardiac transplantation.

Hirsutism, upper extremity tremors, gastrointestinal ileus and constipation, hyperplasia of the gums, and

nasal congestion are nuisances. Hypertension in these patients is a new experience and presumably is related to CyA as it has developed in patients who were previously normotensive. It has been difficult to treat.

### Conclusion

CyA and low-dose prednisone are effective in preventing early morbid rejection of the transplanted heart, and may be superior in that the number of infectious episodes and nonviral infections appears to be less than that associated with the use of Aza and larger doses of steroids.

### References

1. Baumgartner WA, Reitz BA, Oyer PE, et al. Cardiac homotransplantation. *Curr Prob Surg* 1979; 16:51.

2. Pennock JL, Oyer PE, Reitz BA et al. Cardiac transplantation in perspective for the future: survival, complications, rehabilitation, and cost. *J Thorac Cardiovasc Surg* 1981; 83:168-177.
3. Calne RY, Rolbs K, White DJG, et al. Cyclosporin A initially as the only immunosuppressive in 34 recipients of cadaveric organs: 32 kidneys, 2 pancreases, and 2 livers. *Lancet* 1979; 2:1033-6.
4. Starzl TE, Weil R III, Iwatsuki S, et al. The use of cyclosporin A and prednisone in cadaver kidney transplantation. *Surg Gynecol Obstet* 1980; 151:17-26.
5. Starzl TE, Klintmalm GBG, Porter KA, et al. Liver transplantation with the use of cyclosporin A and prednisone. *N Engl J Med* 1981; 305:266-269.
6. Lower RR, Shumway NE. Studies on orthotopic transplantation of the canine heart. *Surg Forum* 1960; 11:18.
7. Billingham ME. Diagnosis of cardiac rejection by endomyocardial biopsy. *Heart Transplantation*. 1981; 1:25-30.
8. Singh G, Rabin BS. Positive warm T-cell crossmatch in cardiac transplantation: with transient vasculitis and without hyperactive rejection. *Transplantation* (in press).
9. Dummer JS, Hardy A, Ho M. Infections in kidney, heart, and liver transplant patients on cyclosporin A. (in press).

### DISCUSSION

DR. ROBERT W. ANDERSON (Minneapolis, Minnesota): In a similar period of time, since approximately February 1981, we have also been interested in using cyclosporin A in cardiac transplantation. Our decision to use this drug was based on a prospective randomized study in our renal transplant patients, and consists of 126 patients with renal transplants who have received cyclosporin A.

Our cardiac transplants in this period have included seven patients, two of whom were children, one seven years old and one 11 years old, in whom we did not think that we should use cyclosporin because we had little experience at that time in younger patients. In the five adult patients, however, we have used cyclosporin, and I think our experience has been comparable with these authors'.

We have found that the time of hospitalization, the incidence of rejections, the cost of the procedure, and the general outcome have been excellent. One of these patients did die of an infectious complication late after operation.

We feel that cyclosporin has a great deal to offer. There are many problems that come up with it, and this would lead to one of my questions. Many of the patients who were operated on were quite sick and had evidence of renal and hepatic failure before operation. They demonstrated continuing renal dysfunction and hepatic dysfunction after operation which we felt was partially related to the use of cyclosporin A. For that reason, we have now switched to conventional immunosuppression for the first week in the immediate postoperative period, and then have gone to the use of cyclosporin.

I was wondering if the authors have experienced a similar problem with early nephro and hepatic toxicity, and whether they feel that this is going to be much of a problem.

The second question that I would ask of them is whether they have found the conventional criteria of rejection, which is usually voltage decrease on the electrocardiogram, has been less helpful to them in the cyclosporin patients when compared with their earlier patients who were treated with conventional immunosuppression.

We find that endocardial biopsy seems to be the only good, valid way of predicting rejection in these patients, and that the use of pe-

ripheral T-cell values and also the use of electrocardiographic criteria are far less valuable.

DR. BARTLEY P. GRIFFITH (Closing discussion): We used Cyclosporin A for immunosuppression in the eight-year-old girl who received an orthotopic transplant. While the oncogenic properties of Cyclosporin A may become an especially significant problem for youthful recipients, we believed that the known problems associated with the use of prednisone at doses of 1 to 0.5 mg/kg/day impose a known substantial morbidity. We feel that lower doses of prednisone and Cyclosporin A may be a better alternative.

Renal toxicity associated with cardiac transplantation and Cyclosporin A has been common, and at times a difficult problem. We have made a strong effort to keep our immunosuppressant regimen of Cyclosporin A and low-dose prednisone pure and thus have not routinely substituted for Cyclosporin A. We are quick to decrease Cyclosporin A to doses of 5 mg/kg/day if urine output falls, hyperkalemia occurs, and if creatinine rises abruptly. In a few patients we have discontinued Cyclosporin A for 12 hours. In one patient, Cyclosporin A was discontinued for 24 hours, and aggressive rejection occurred. If this situation were to occur again, we would substitute Azothiaprime after 24 hours.

Conventionally, electrocardiographic voltage, T-cell rosettes, and endomyocardial biopsy have been used for the detection of graft rejection. In the Cyclosporin A group, the changes in electrocardiograph voltage frequently did not precede or even mirror marked histologic changes evident in the endomyocardial biopsy. This may, in part, be due to the presence of less myocardial edema observed in Cyclosporin A-treated patients. Because rabbit antithymocyte has not been used in our series, T-cell rosettes have remained elevated and did not change in any observable pattern during a rejection episode. Recently, we have measured peripheral T-cell helper and suppressor ratio, but changes in the ratio have not correlated with histologic or clinical rejection. The endomyocardial biopsy has been obtained routinely at weekly intervals for the first four weeks following transplantation and, therefore, as the clinical situation may dictate. The results of the biopsy have directed the use of pulse therapy with steroids.