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CYCLOSPORIN A AND STEROID THERAPY IN SIXTY-SIX CADAVER KIDNEY RECIPIENTS

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THE INADEQUACIES of conventional immunosuppression with azathioprine and prednisone have been serious enough to prevent the full exploitation of organ transplantation procedures. The prospect of improving the situation was dependent upon new immunosuppression techniques. In 1976, Borel and associates (2, 3) described the immunodepressive properties in mice, rats and guinea pigs of an extract from the fungi *Cylindrocarpum lucidum* and *Trichoderma polysporum*. Cyclosporin A suppressed cellular and humoral immunity without bone marrow depression or other prohibitive organ toxicity.

Clinical trials were begun in 1978 by Calne and co-workers (5, 7) in England with encouraging results. In late 1979, cyclosporin became available for preliminary testing in the United States (28). We report herein a learning experience with this drug in 66 consecutive human recipients of 67 cadaveric renal homografts for whom follow-up periods of nine to 18 months are now available.

METHODS

The mean age of the 66 patients was 39.2 ± 9.9 , S.D., years, a range of 18 to 61 years. There were

12 women and 54 men. Three of the patients had diabetes. Six were carriers of HbsAg virus, although only one patient had other evidence of hepatic disease. Three patients had malignant hypertension which was thought to have caused the renal failure. Two patients had coronary artery disease and one patient had cardiomyopathy. Two other recipients were suspected of having coronary artery disease, the severity of which was underestimated preoperatively.

The transplantations were primary in 57 patients. In the other nine, the patients were undergoing their second or third transplantation. No attempt was made to transfuse deliberately the recipients in advance of the operation. Many of them were referred from nephrology centers at which transfusion had been avoided.

The matches of the recipients with their donors were poor. The number of mismatches at the HLA-A and B loci averaged 3.3 ± 0.7 , S.D., and only ten of the 66 patients had as few as two mismatches. At the D-related locus, there were no perfect matches in the 58 recipients for whom this information was available.

The serums of all 66 recipients were analyzed for antibody content. Eleven of the primary and six of the secondary or tertiary graft recipients had warm anti-T or anti-B lymphocyte antibodies against more than 20 per cent of a panel obtained from 30 volunteers. Eight of the primary and three of the secondary or tertiary graft recipients had positive B-warm cross matches with the lymphocytes of their donors. There were no examples of transplantation against donor spe-

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TABLE I.—CAUSE OF DEATH AND ITS RELATION TO IMMUNOSUPPRESSION

Patient No., Age, yr. Sex	Pre-existing medical conditions	Cause of death	Days post- operatively	Renal function before death, creatinine, mgm. per cent	Relation of immunosuppression to death
1 45 F	Chronic aggressive hepatitis, HbsAg+	Cerebral hemorrhage, recent pulmonary no cardia resolved	335	2.9	None
15 28 M	Pulmonary and pleural granulomatosis, probably histoplasmosis	Pulmonary emboli, Pneumocystis carinii pneumonitis	110	2.3	Yes
18 46 M	Coronary atherosclerosis	Intrathoracic hemorrhage after coronary artery bypass	34	2.0	None
21 29 M	None	Intra-abdominal and intracranial no cardia infection; pancreatic necrosis	222	Anephric	Yes
27 29 M	None	Pneumonia; seizures with aspiration	80	Anephric	Yes
40 39 M	None	Pneumonitis, pneumocystis carinii plus bacterial	154	3.0	Yes
45 53 M	Duodenal ulcer in remission	Gastrointestinal hemorrhage; systemic infection	109	2.4	Yes
58 48 M	Coronary atherosclerosis	Anaphylactic reaction to coronary angiography contrast medium	20	1.9	None
65 60 M	None	Pneumonitis, Pneumocystis carinii	82	4.2	Yes

M, Male; F, female; HbsAg, hepatitis B surface antigen

cific T-warm antibodies which cause, as shown by Terasaki and colleagues (31), hyperacute rejection.

Many of the first patients in our series (28) had pretreatment with thoracic duct drainage, lymphapheresis or cyclosporin A. The pretreatment time was from a few days to almost three months and was well tolerated. However, the practice of pretreatment was discontinued because the results were not better than when immunosuppression with cyclosporin A was begun a few hours before operation.

In the first part of the series, prednisone was withheld postoperatively until there were manifestations of rejection. When it became obvious that rejection occurred in about two-thirds of patients, treatment was standardized.

On the day of, or the day before, operation and after, cyclosporin A was given at a dose of 17.5 milligrams per kilogram per day. This was continued daily for two months, if possible. This dose was decreased at the end of that time, or before in the event of toxic side-effects, to the 10 milligrams per kilogram per day range. For adults, predni-

sone was begun at a dose of 200 milligrams on the day of operation, with decrements of 40 milligrams for the next four days. On day 5, the dose was reduced from 40 to 20 milligrams. After this, weaning from the 20 milligrams per day was on the basis of the clinical course. Deviations from this plan were made if dictated by complications postoperatively, including the supervision of rejection. Rejections were treated with a 1 gram bolus of hydrocortisone plus a repeat five day course of high dose prednisone given orally, using reductions of 40 milligrams a day from a beginning level of 200 milligrams.

Tissues from renal homografts were examined with conventional histopathologic techniques. Special studies were performed for those patients who were suspected of having lymphomas. In these two patients, no fresh or frozen tissue was available. Fixed tissue was preserved for study by light microscopy, electron microscopy and immunoperoxidase techniques. For the immunoperoxidase studies, the specificity of the antisera was established by the blocking and hemagglutination techniques of Mason (18), Taylor and

TABLE II.—PATIENTS CHANGED FROM CYCLOSPORIN A TO AZATHIOPRINE

Patient No.	Graft function prior to change, creatinine, mgm. per cent	Present graft function after change, creatinine, mgm. per cent	Time of change after transplant, mos.	Indication for therapeutic change
2	2.3	2.5	13	Hepatotoxicity
3	3.1	1.4	8	Nephrotoxicity plus hepatotoxicity
9	3.6	Graft loss 2½ months later	6	Nephrotoxicity
12	4.6	2.8	4	Nephrotoxicity
14	3.6	2.1	10	Nephrotoxicity
21	3.6	Graft loss 2 weeks later	5	Nephrotoxicity

Burns (30) and Zulman and collaborators (34). Immunoenzymatic staining was performed on paraffin embedded tissue sections, using either the peroxidase antiperoxidase technique of Sternberger and co-authors (29) or the labeled antigen technique of Mason and Sammons (19). Formalin fixed material was treated with trypsin. X-chromatin and Y-chromatin counts were performed upon the tumor tissue using Feulgen stained preparations and quinacrine fluorescence microscopy, as described by Curran and Gregory (10).

Serums from these two patients were titrated for antiviral capsid antigen, IgG of Epstein-Barr virus by the indirect immunofluorescent method of Henle and Henle (11) and for antiviral capsid antigen IgM after sucrose density fractionation. Antibody to herpes simplex virus and cytomegalovirus was sought by complement fixation.

The clinical objectives of the trial were to learn the optimum way to use the drug and to see if the results were as good as, or better than, in the past with established methods of immunosuppression. Thus, randomized contemporaneous controls were not obtained. However, the results with primary cadaveric transplantation were compared with those during the preceding three years, using

TABLE III.—PRESENT GRAFT FUNCTION IN LIFE-SUSTAINING KIDNEYS

Serum creatinine value, mgm. per cent	No. of patients	Mean cyclosporin dose mgm./kgm./day ± S.D.	Mean prednisone dose mgm./day ± S.D.
≤1.5	9	8.3±2.1	14.4±3.7
1.6-2.5	26	7.8±1.8	17.3±2.9
2.6-3.5	15	7.6±1.7	18.0±3.6
≥3.6	2	4.8*, 6.5†	10, 20

* Recurrent oxalosis.

† Has acute rejection. Cyclosporin dose recently was increased from 4.8 to 6.5 milligrams per kilogram per day.

conventional immunosuppression of azathioprine and prednisone, with or without antilymphocyte globulins, and conventional immunosuppression plus thoracic duct drainage preoperatively and postoperatively (27). Preoperatively, the lymphoid depletion was for at least 28 days.

RESULTS

Patient Survival

Nine of the 66 patients died from 20 to 335 days after transplantation (Table I). At the time of death, five of the nine patients had good, or excellent, graft function. Two of these five recipients died as a result of instrumentation for the diagnosis or treatment of coronary atherosclerosis. The first of these patients had a fatal anaphylactic reaction to the contrast medium. The second patient had a fatal hemorrhage after a coronary artery bypass. A third patient of the five with good graft function died suddenly of a cerebral hemorrhage 11 months after transplantation. The deaths of these three patients were not considered to be related to immunosuppression.

Infection with the opportunistic organisms commonly reported with conventional immunosuppression was a major factor in the deaths of six patients. Rejection had been diagnosed in all six, and increases in the dosage of prednisone had been used in unwise efforts to save the grafts.

None of the patients died after cadaveric retransplantation. The actuarial patient survival of recipients of first kidneys has been slightly better than in the actual survival of retrospective controls (Fig. 1), but not significantly so.

Kidney Survival

Follow-up periods are now nine to 18 months for the 57 patients still living. Twenty-three survivors are alive more than a year. Fifty-two of the original 66 patients are free of dialysis.

Primary cadaveric transplantation. Of the 57 kidneys transplanted into 57 recipients, nine were placed in recipients who died and two more were lost to rejection. Thus, 80.7 per cent of the grafts are supporting life. The actuarial graft survival data are shown in Figure 2 in comparison with that actually achieved with other techniques of immunosuppression.

Cadaveric retransplantation. Of ten kidneys transplanted into nine recipients, six are functioning after 17, 16, 15, 14, 12 and 11 months. Three organs were lost to rejection. The fourth was removed because of complete ureteral necrosis, after which retransplantation was successfully carried out.

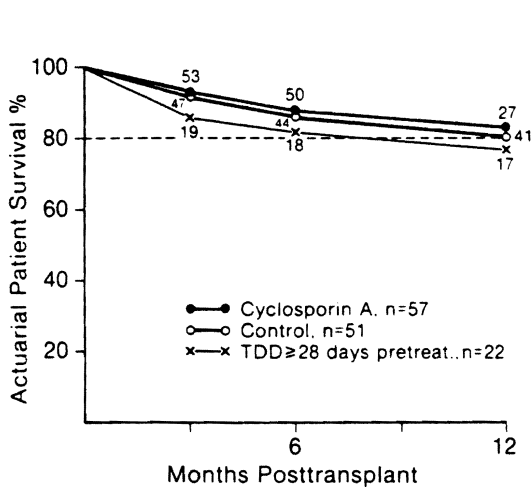


FIG. 1

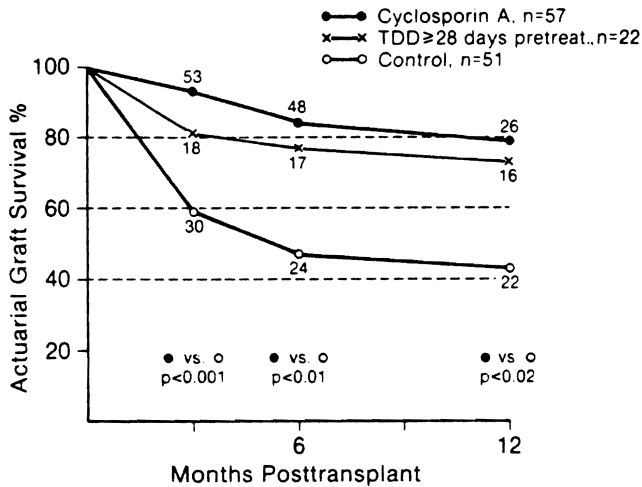


FIG. 2

FIG. 1. Denver series of primary cadaveric kidney transplant. One year actuarial patient survival of 57 recipients of primary grafts being treated with cyclosporin A and prednisone. Actual follow-up time is nine to 18 months. The results are compared with the actual one year patient survival using thoracic duct drainage preoperatively and postoperatively plus conventional immunosuppression and conventional immunosuppression alone, control. *TDD*, Thoracic duct drainage.

FIG. 2. Denver series of primary cadaveric kidney transplant. One year actuarial graft survival of 57 primary cadaveric grafts under treatment with cyclosporin A and prednisone. Actual follow-up time is nine to 18 months. There were no exclusions. The results are compared with the actual one year survival of primary cadaveric kidneys under optimal treatment with thoracic duct drainage plus conventional immunosuppression and conventional immunosuppression alone, control. The p values were derived with the Student's t test. *TDD*, Thoracic duct drainage.

Change to Azathioprine

After four to 13½ months, cyclosporin A was stopped in six patients (Table II). In each instance, nephrotoxicity was suspected. Within 13 days to ten weeks, two of the recipients rejected their kidneys. The other four have had stable or improved renal function in the ensuing 12, 11, eight and four months.

Renal Function

The serum creatinine levels in the patients who died are given in Table I. Five living patients are anephric, three being in the retransplantation group and two, in the primary transplantation group. The serum creatinine concentrations in the 52 patients still bearing kidneys are summarized in Table III. More than half of these recipients have satisfactory and stable function, as defined by a serum creatinine value of less than 2.5 milligrams per cent. As previously reported by Calne and associates (5), a number of patients with clinically good results have slightly abnormal renal function.

Renal Histopathology

Eleven kidneys became available for study 14 to 335 days after transplantation. In seven, immunosuppression had been stopped for a significant period previously (Table IV), and six of

these grafts showed evidence of rejection. In four, it was acute, superimposed in one instance upon chronic rejection, in one instance it was chronic, and, in another instance, acute rejection was just commencing. The seventh kidney was normal 11 days after stopping immunosuppression, except for a few fibrin thrombi in glomerular capillaries and in arterioles.

Four kidneys came from patients who had received continuous immunosuppression. Two of these showed changes of chronic rejection; in one patient, there was mild cellular infiltration, and in the fourth, there was no evidence of rejection.

An unusual feature in three of the seven grafts which showed signs of acute rejection was the presence of eosinophils in the interstitial cellular infiltrate. One graft showed patchy acute tubular necrosis, but there was no morphologic evidence of a specific cyclosporin induced tubular lesion.

Hospitalization and Morbidity

Duration of hospitalization in the last 30 primary cadaver recipients was 15±6, S.D., days, a range of seven to 35 days. The total hospitalization in the retrospective control groups was 57±21, S.D., a range of 22 to 151 days with conventional immunosuppression and 74±13, S.D., days, a range of 51 to 135 days, after optimal thoracic duct drainage treatment.

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TABLE IV.—HISTOPATHOLOGY OF 11 RENAL HOMO-
GRAFTS

Patient No.	Conditions of sampling	Time of sampling after transplant days	Days		Pathologic findings
			without CyA/azathioprine before sampling		
1, P	Autopsy	335	0		Some patchy proximal tubular necrosis. No evidence of rejection
9, P	Nephrectomy	291	139/5		Chronic rejection with mononuclear cell infiltration, obliterative arterial lesions and transparent glomerulopathy
12, R	Nephrectomy, ureteral necrosis	16	0		Minimal cellular infiltration and no vascular lesions
15, P	Autopsy	110	11		No evidence of rejection. Few fibrin thrombi in glomerular capillaries and in arterioles
19, R	Nephrectomy	46	1		Chronic rejection with mononuclear cell infiltration and obliterative arterial lesions
21, P	Nephrectomy	155	27/8		Acute cellular and humoral rejection superimposed on old chronic rejection with obliterative arterial lesions
27, P	Nephrectomy	14	25		Acute rejection with secondary oxalosis.
40, P	Autopsy	154	11		Minimal cellular infiltration with rare arteriolar necrosis
51, R	Nephrectomy	25	11		Acute cellular rejection
55, R	Nephrectomy	44	1		Chronic rejection with mononuclear cell infiltration and obliterative arterial lesions
57, P	Nephrectomy	147	36		Necrotic kidney secondary to acute rejection

P, Primary transplant; R, retransplant; CyA, cyclosporin A.

There was one deep wound infection. In addition to the infections in the patients who died, there were six examples of pneumonitis. These included three pneumocystis carinii, one example of nocardia and two of undetermined cause. One patient had an abscess of the lung which was treated with left lower lobectomy after immunosuppression was stopped. Eight patients had herpes simplex at some time. There were no

examples of herpes zoster. Miscellaneous infections included histoplasmosis, amebic colitis and three examples of pneumocystis carinii in addition to the patients who had this diagnosis at autopsy.

The well-being of patients treated with cyclosporin A was remarkable, mainly because of the low dosages of prednisone, which usually were in effect by the end of five days. Hirsutism, gum hyperplasia, flushing and paresthesias after drug ingestion and tremors, as described by Calne and colleagues (7) and us (28), were minor annoyances. Liver function abnormalities were seen in 13 of the 66 patients, but these receded with dosage reduction in all but one instance. Cyclosporin was changed to azathioprine in the exceptional patient, 13 months after transplantation.

Nephrotoxicity of cyclosporin A was suspected in 15 of the patients, while dosages of 17.5 milligrams per kilogram per day were being given. All improved when dosages were lowered. The distinction between nephrotoxicity and rejection was too imprecise to permit the acquisition of decisive data about the true incidence of nephrotoxicity.

Lymphoproliferative Complications

Patient 8 was a 25 year old woman in whom perforation developed in the mid-small intestine 157 days after transplantation. She was treated with segmental intestinal resection. Her cyclosporin dose was reduced from 15.8 to 5.9 milligrams per kilogram per day. She has had no known recurrence in the ensuing nine months.

In the base of the perforated ulcer, there were B cells, as described by Lukes and Collins (16) in their classification scheme for lymphoproliferative disorders. Determination of intracellular immunoglobulins by immunoperoxidase techniques indicated that the B cells were polyclonal, 95 per cent of the cells producing alpha and 5 per cent, gamma heavy chains. The kappa light chain to lambda light chain ratio was 6:1. The B cells showed female chromatin markers, that is, they were of host origin because the donor was male. The lesion was officially designated a lymphoproliferative reaction, not a lymphoma.

Patient 15 died of pulmonary emboli and pneumocystis pneumonia 110 days after transplantation. At autopsy, an incidental finding was small nodular deposits of B cells in the retroperitoneal and para-aortic lymph nodes, in the spleen, in the liver and in the heart. Most of the deposits were necrotic. Immunoperoxidase techniques revealed that the B cells were monoclonal and that many of them were producing mu heavy

chains and kappa light chains. The origin of the cells could not be determined because the host and donor were of the same sex.

In both patients, the stored serums before and after renal transplantation were examined for antibodies against the Epstein-Barr virus. In both instances, the antiviral capsid antigen titer rose significantly after renal transplantation (Tables V and VI). In Patient 8, this was the result of a primary infection (Table V). Patient 15 had antibody before transplantation, suggesting reactivation of Epstein-Barr virus. Neither patient showed increased antibody production to cytomegalovirus or herpes simplex virus.

DISCUSSION

The need to develop better immunosuppressive therapy can be illustrated by the multicenter compilations of data of Opelz and co-workers (22) and McDonald and co-authors (20). With conventional immunosuppression, they reported that less than half of the primary cadaveric grafts were functioning at the end of the first postoperative year. The outlook after cadaveric retransplantation has been even less encouraging (13). Even with success, the quality of life has too often been degraded by the need for chronic treatment with high dosages of steroids.

The consequence has been a reluctance by many responsible nephrologists to advise cadaveric renal transplantation or a disinclination of their patients to accept such a recommendation. The economic impact has been staggering as the number of patients maintained in renal dialysis centers has swelled without a commensurate decompression by transplantation. Efforts to improve the situation with tissue matching or by adding antilymphocyte globulin, total lymphoid irradiation and thoracic duct drainage to azathioprine-prednisone therapy have been of questionable efficacy on one hand or too expensive or inconvenient on the other for general applicability, or both.

Thus far, the trials with cyclosporin A have escaped such disillusionment. However, they have raised questions about the optimal use of this agent, which will have to be taken into consideration by those planning randomized trials. The most persistent of the questions has been whether or not to use cyclosporin A as the sole immunosuppressive therapy, as practiced by Calne and collaborators (5, 6, 7) or to combine it from the beginning with prednisone, as we have recommended (26, 28). The view of Calne was based, in part, upon his recognition that cyclosporin A

TABLE V.—ANTIBODY CHANGES IN PATIENT EIGHT

Date, 1980	Antiviral capsid —antigen of Epstein-Barr virus—		Paul Bunnell test
	IgG	IgM	
Jan. 3	<8	neg.	<10
10	<8	neg.	<10
17	<8	neg.	<10
24	<8	neg.	<10
31	<8	neg.	<10
	renal transplant		
Feb. 7	<8	neg.	<10
14	<8	neg.	<10
21	16	pos.	40
27	febrile illness		
28	64	pos.	80
July 5	64	pos.	<10
	lymphoma resected		
10	64	pos.	<10
17	64	pos.	<10

possessed nephrotoxic properties which could mimic rejection and, thereby, precipitate steroid therapy for which there was no indication. In about half of our kidney recipients, the clinical diagnosis of rejection has been made either early or late. Renal specimens were not taken for biopsy. However, structural signs of rejection almost always were present in kidneys retrieved at autopsy or by graft nephrectomy. Moreover, in recipients of orthotopic livers in whom graft biopsies were systematically obtained, histopathologic evidence of rejection was found in the majority of patients (26). With both organs, the rejections were less violent than with conventional immunosuppression, and usually, they were highly responsive to adjustments of steroids.

Because of the issue of nephrotoxicity, Calne and associates (5, 6, 7) recommended delaying therapy with cyclosporin A until a vigorous diuresis was in effect, in the belief that many of the early anurias in their series were caused by cyclosporin A rather than by immunologic factors. Because our observations were interpreted conversely, we have begun cyclosporin A before the operation with the intention of having a therapeutic blood level when the graft was vascularized. There has been no obvious disadvantage from this practice.

Nevertheless, nephrotoxicity as a management problem has been established unequivocally, since the early reports of Calne and co-workers (5, 7). Powles and associates (24) have reported azotemia in bone marrow recipients, and we have seen the same thing after successful orthotopic liver transplantation (15, 26). Fortunately, the complication usually has reversed with a reduction of the cyclosporin A dosage (15, 26, 28). In kidney recipients, the interface between effective immunosuppression and nephrotoxicity may be

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TABLE VI.—ANTIBODY CHANGES IN PATIENT 15

Date	Antiviral capsid antigen of Einstein-Barr virus, IgG
24 Oct. 1979	8
19 Feb. 1980	renal transplant
21 Feb. 1980	8
28 Feb. 1980	8
6 Mar. 1980	8
15 May 1980	16
22 May 1980	64
29 May 1980	256
8 June 1980	Died lymphoma diagnosed at autopsy

difficult to define. We have tried to maintain the potentially nephrotoxic daily dose of 17.5 milligrams per kilogram for the first two postoperative months, even if there is imperfect, but life-sustaining, renal function, believing that a subsequent reduction will be less apt to allow rejection and knowing that nephrotoxicity usually can be relieved by a reduction in the dosage at that time.

Even long after transplantation, minor azotemia and hypercreatinemia seen in many patients receiving cyclosporin A may represent a low grade nephrotoxicity which does not vitiate the value of the drug. Since results of none of the histopathologic studies showed evidence by light or electron microscopy of a specific lesion induced by cyclosporin, we have concluded that cyclosporin A can be used for chronic therapy. As a last resort, a change to azathioprine can be made, but at a considerable risk of subsequent rejection.

Most of the other side-effects of cyclosporin A have not been serious, including gum hyperplasia, tremor and regional flushing or vague abdominal discomfort just after drug ingestion. Although hepatotoxicity is seen in about one-fifth of the patients, this has been serious enough to necessitate a change to azathioprine in only one patient, more than a year postoperatively.

The most publicized question about cyclosporin has concerned its potential oncogenicity. It has been known for 15 years that the price of conventional immunosuppression is an increased incidence of *de novo* tumors. In the recent collection of Penn (23), approximately one-third were lymphomas. Thus, early reports by Calne and colleagues (5) of lymphomas in patients treated with cyclosporin A were neither surprising nor dismaying. There was one example in the present series. It was not responsible for mortality. To our knowledge, no epithelial tumors have been seen in renal recipients. As experience with cyclosporin A has accumulated worldwide, the spector

of this drug being a spectacular tumor producer has receded.

Most malignant lymphomas of B-cell type are monoclonal and produce immunoglobulin of a single light chain type. As described by Warnke and collaborators (33), IgM is the most frequently expressed heavy chain and Patient 15 in our series conforms to this pattern.

Several of the so-called lymphomas that have occurred after organ transplantation resemble the lesion found in Patient 8 in our study in that they have been reported as polyclonal by Borzy and co-authors (4) and Hertel and associates (12). Other post-transplant lymphomas reported by Crawford and colleagues (9) and Warnke and co-workers (33) have not borne immunoglobulin, and it has not been possible to determine their clonality.

Reactivation of Epstein-Barr virus after renal transplantation is common, and as in Patient 15 in our series, this has occasionally been associated with the discovery of an immunoblastic sarcoma, as summarized by Marker and collaborators (17). A primary Epstein-Barr infection after renal transplantation is rare, and it is interesting that, of the few instances recorded, one has been said by Nagington and Gray (21) to have been associated with lymphoma. The findings were similar to those of Patient 8 in our study in whom the final diagnosis was immunoproliferative reaction rather than lymphoma. In two immunoblastic sarcomas in transplant recipients studied by Nagington and Gray (21) with Epstein-Barr virus deoxyribonucleic acid cytohybridization, Epstein-Barr virus deoxyribonucleic acid was found to be present in a significantly high concentration in the lymphoma. In a patient studied by Crawford and co-authors (9), Epstein-Barr virus nuclear antigen was demonstrated in the tumor cells.

Unfortunately, these latter investigations could not be performed upon the patients in our study. The increased antiviral capsid antigen observed in the patients in our series with lymphoproliferative disorders was not part of a general increase in antibody production. The same thing was noted by Nagington and Gray (21) who wondered if the explanation might be a specific depression by cyclosporin A of the suppressor T cell related to Epstein-Barr virus infected lymphocytes. If this is correct, the defective suppressor cell function might then permit the simultaneous expression of many clones of B cells, resulting in a polyclonal immunoblastic lesion. Bird and McLachlan (1) and Crawford and associates (8)

provided some evidence *in vitro* to suggest that cyclosporin A may specifically delete or inactivate T cells, but little is known of its effect *in vivo*.

In an earlier report by Iwatsuki and colleagues (14) it was asked if the so-called lymphomas developing under conventional immunosuppression had the same lethal behavior as those in non-immunosuppressed patients. The same question must be raised in patients treated with cyclosporin A. Only time will tell whether or not these lymphoproliferative disorders will behave in the same way as apparently identical tumors in non-immunosuppressed individuals. So far, in our experience and in that of Calne and co-workers (6), no deaths have been attributable to *de novo* malignant lesions which rose under cyclosporin A therapy. In our hands, the incidence of lymphoma has been less than 1 per cent in a total experience now totaling 123 patients, the only unequivocal example being patient 15 herein reported.

Unless some other, as yet unrecognized, side-effect emerges to limit the usefulness of cyclosporin A, this agent should permit significant advances in whole organ transplantation. The early results in our preliminary trial were as good as, or better than, in any previous series of cadaveric transplantations done at our institution, in spite of the inclusion of many recipients who were at higher than average risk because of advanced age, vascular disease, hepatitis carrier state and diabetes mellitus. These patients participated in the learning process with a new technique and one which was in no sense standardized until near the end of the trial. Yet, 79 per cent of the recipients of randomly matched cadaveric organs are dialysis-free and, in most instances, with good or excellent renal function after nine to 18 months.

Five patients are anephric and nine have died. It is evident that most of the deaths were preventable. The patients with coronary artery disease should have been treated more aggressively before transplantation. Most of the infectious deaths were attributable to unwarranted persistence at salvage of the kidneys. The lesson has been taught by Salviatierra and collaborators (25), Tilney and co-authors (32) and many others using conventional immunosuppression.

SUMMARY

From nine to 18 months ago, 66 patients were given 67 randomly matched cadaveric kidneys with cyclosporin A and steroid therapy. Nine of the recipients were undergoing retransplantation. The over-all kidney survival rate to date has been 77.6 per cent, and 78.8 per cent of the recipients

are dialysis-free. The patient mortality in this learning phase was 13.3 per cent. Nephrotoxicity, hepatotoxicity and other side-effects of cyclosporin A could usually be dealt with by dosage adjustments, making feasible the chronic use of this agent. One B-cell immunoblastic sarcoma was encountered which was monoclonal. It was not responsible for death. Another patient had a perforation of the intestine from a lymphoproliferative reaction in which the B cells were polyclonal. After jejunal resection a year ago, there were no further complications. This lesion was not classified as a lymphoma. Both lymphoproliferative lesions were associated with a rise in antibody to viral capsid antigen of Epstein-Barr virus. Results of this study have verified the effectiveness and relative safety of cyclosporin A with steroids for immunosuppression in human recipients of cadaveric kidneys.

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