THE USE OF CYCLOSPORIN A AND PREDNISONE IN CADAVER KIDNEY TRANSPLANTATION

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CYCLOSPORIN A, the most promising new immunosuppressive agent of recent years, is an extract from the fungi Cylindrocarpon lucidum and Trichoderma polysporum. It was discovered by Dreyfuss and associates (10), characterized biochemically by Ruegger (17) and Petcher (15) and their associates, and shown to be immunosuppressive by Borel and colleagues (2, 3, 4). The studies by Borel and colleagues (2, 3, 4) of cyclosporin A in mice, rats and guinea pigs were quite complete. With multiple test systems, including skin homotransplantation, Borel and colleagues (2, 3, 4) showed that cyclosporin A depressed humoral and cellular immunity, that it had a preferential and quickly reversible action against T lymphocytes and that these effects were not accompanied by bone marrow depression or other prohibitive organ toxicity. The ability of cyclosporin A to prevent or delay rejection of hearts, kidneys, livers or pancreases was promptly shown in rats, rabbits, dogs and pigs by Kostakis (13), Calne (7, 8, 9) and Green (11) and their associates.

An evaluation of cyclosporin A in human recipients of kidneys, pancreases and livers has been reported by Calne and collaborators (5, 6). The ability of the drug to prevent irreversible rejection without ancillary steroid therapy was striking. However, Calne and co-workers (5, 6) concluded that unexpectedly severe nephrotoxicity was responsible for a high incidence of anuria shortly after renal transplantation and for abnormal late graft function in the majority of the kidney recipients. Furthermore, the administration of other drugs, including steroids, proved to be so dangerous that their chronic use was thought not to be advisable.

Our own early observations in 22 consecutive cadaveric renal transplant recipients treated with cyclosporin A have been interpreted differently. We have concluded that many of the early and delayed perturbations of kidney graft function in the patients in our series were manifestations of immunologic rejection rather than drug toxicity, that the appropriate treatment frequently was with steroids and that the maximum short term and long term value of cyclosporin A could not be realized without such combination therapy. So far, cyclosporin A and prednisone have been safe when used together, even in patients who were prepared for transplantation by prolonged thoracic duct drainage.

METHODS

The mean patient age was 37±8, S.D., years, with a range of 26 to 48 years (Table I). The 22 recipients included four who were undergoing retransplantation after the rejection at an earlier time of one or more kidneys. Two of the patients had diabetes.

The random matches of the recipients with their cadaveric donors were poor. In the HLA-A and HLA-B loci, the average number of mismatches was 3.0±0.8, S.D., a range of 2 to 4. At the DR locus, there was only one perfect match in the 14 recipients for which this information was

TABLE 1.—INFORMATION ON TWENTY-TWO PATIENTS WHO WERE TREATED WITH CYCLOSPORIN A FROM TWO TO FOUR AND ONE-HALF MONTHS AGO

Group headers: *Graft failure in first 4½ mos.* spans Time / Steroid responsive / ↑Cyclosporin A responsive / ↓Cyclosporin A responsive. *Liver toxicity* spans Onset time / Dose of cyclosporin A / Maximum bilirubin. *Renal function at present* spans BUN / Creatinine. *Immunosuppression at present* spans Prednisone / Cyclosporin A.

Patient No.	Age, yrs.	Sex	Days of pretreatment	Early diuresis	Time	Steroid responsive	↑Cyclosporin A responsive	↓Cyclosporin A responsive	Onset time, weeks	Dose of cyclosporin A	Maximum bilirubin, mgm. per cent	BUN, mgm. per cent	Creatinine, mgm. per cent	Prednisone, mgm./day	Cyclosporin A, mgm./kgm./day	Follow-up, mos.
PRETREATMENT WITH THORACIC DUCT DRAINAGE, TDD																
1	45	F	46	Yes	4 Mos.	Yes			1	17.5	2.7	35	1.5	20	9.4	4½
2	43	M	31	Yes	2 Days	Yes						27	1.8	15	10.0	4½
					6 Weeks	Yes										
3	27	M	27	Yes	9 Weeks	Yes		Yes	6	14.0	1.9	30	2.1	10	10.8	4
4	27	F	25	Yes	1 Day	Yes						40	1.8	15	7.4	4
					3 Mos.			Yes								
5*	39	M	81	Yes	3 Days	Yes						53	2.4	20	8.0	3
					8 Weeks			Yes								
6*	42	M	40	Yes								34	1.4	15	7.6	3
8	26	F	64	Yes								35	1.2	5	17.5	3
9†	40	M	54	Yes								41	2.3	15	7.5	2
10	24	M	84	Yes	5 Weeks	Yes						60	2.4	20	15.0	2
					9 Weeks	Yes										
11	48	M	14, TDD; 6, CY-A	Yes	3 Weeks	Yes	Yes					30	2.0	15	9.2	2
					9 Weeks	Yes		Yes								
12*	37	M	24	Yes	Ureter necrosis, graft removed							Retransplanted				2
PRETREATMENT WITH CYCLOSPORIN A, CY-A																
7	44	M	1	Yes	4 Days	Yes		Yes				31	1.6	20	10.0	2½
13	45	M	18	Yes	4 Weeks	Yes			4	17.5	6.6	26	2.1	20	15.0	2½
					5 Weeks		Yes									
14‡	46	M	5	Yes	4 Days	Yes						18	1.4	10	10.0	2½
15	28	M	7	Yes	3 Days	Yes			8	17.5	1.9	58	2.6	20	17.5	2½
16	27	M	8	Yes	3 Days	Yes						52	2.0	25	12.5	2¼
					3 Weeks	Yes										
17‡	42	M	1	Yes	5 Days	Yes						43	1.5	20	15.0	2
					7 Weeks	Yes										
18	46	M	10	Yes	1 Day	Yes						24	2.0	15	8.0	1¼§
19*	27	F	18	Yes	1 Week	No, graft removed on 46 day			4	17.5	2.0	Dialysis				
20	42	F	11	Yes	2 Days	Yes						33	1.8	15	17.5	2
21	29	M	6	Yes	2 Mos.			Yes				60	2.5	25	10.0	2
22	38	M	9	Yes	4 Days	Yes			5	17.5	5.5	33	2.7	15	11.0	2
					5 Weeks			Yes								

*Retransplantation.
†Pretreatment with lymphapheresis.
‡Diabetic.
§Death with functioning graft.
TDD, Thoracic duct drainage.
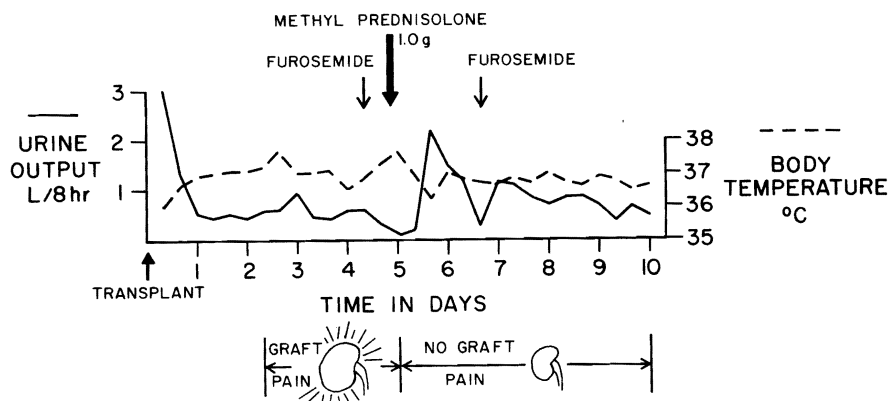CY-A, Cyclosporin A.
BUN, Blood urea nitrogen.

FIG. 1. A typical example of post-transplantation oliguria which became most severe on day 4 in Patient 7. Cyclosporin A in daily doses of 17.5 milligrams per kilogram was begun one day before transplantation. With the apparent rejection, there was progressive graft swelling, pain and tenderness. These findings as well as low grade fever and oliguria were relieved promptly by a single bolus of methyl-prednisolone given intravenously. Nine days later, maintenance dosages of predni-sone were started orally.

available. The serums of seven recipients contained warm cytotoxic antibodies against the B or T lymphocytes, or both, of at least 20 per cent of a panel of 30 normal volunteers (12, 23). No transplantations were carried out across a positive warm T-cell cross match.

Mechanical Lymphoid Depletion

Using previously described techniques (22), ten of the 22 patients had thoracic duct drainage for 14 to 84 days before transplantation (Table I) and for one to 36 days thereafter. The total number of lymphocytes removed ranged from 49 to 376×10^9 with a mean of 140 ± 82, S.D., $\times 10^9$. One recipient had removal of blood lymphocytes by lymphapheresis five times a week for seven weeks. The total number of lymphocytes removed during this time was 94×10^9.

Cyclosporin A Schedule

For the 11 patients prepared with lymphoid depletion, cyclosporin A was given orally six to 12 hours before transplantation in a dose of 17.5 milligrams per kilogram and continued at this dose given orally once daily thereafter. Postoperatively, all recipients ate promptly, making parenteral administration unnecessary.

The 11 recipients not prepared with lymphoid depletion were pretreated instead with daily dosages of cyclosporin A given orally for one to 18 days, as shown in Table I, average 8.7. The daily dose was usually 17.5 milligrams per kilogram.

Two months after transplantation, or sometimes before this, if nephrotoxicity was suspected, the patients were considered for an adjustment of the maintenance doses of cyclosporin A but only in some were the changes actually made. The present daily dosages of cyclosporin A after two to four and one-half months are summarized in Table I.

Rejection and Steroid Therapy

Steroid therapy was not given initially in eight patients, and in 14 others, a single intravenous bolus of 1 gram methylprednisolone was given during transplantation. Maintenance steroids were started later, usually because rejection was suspected.

Rejection was diagnosed if renal failure recurred in the early postoperative period in the absence of technical complications. Declining urine volume, graft swelling with wound tenderness and fever were signals for urgent therapy with intravenously administered 1 gram doses of methylprednisolone or 0.1 to 1.0 gram doses of hydrocortisone. The presence of only one of these three findings was not always accompanied by increases in serum creatinine and blood urea nitrogen values. However, recurrent uremia almost always could be documented if two, or all three, components of the triad were present. Radionuclide scanning was performed at regular intervals and was particularly helpful in observing the course of patients whose grafts went through periods of nonfunction.

When rejection was diagnosed, the first patients were treated with steroid bolus therapy alone (Figs. 1 and 2). Later in the series, the intravenous bolus of methylprednisolone or hydro-
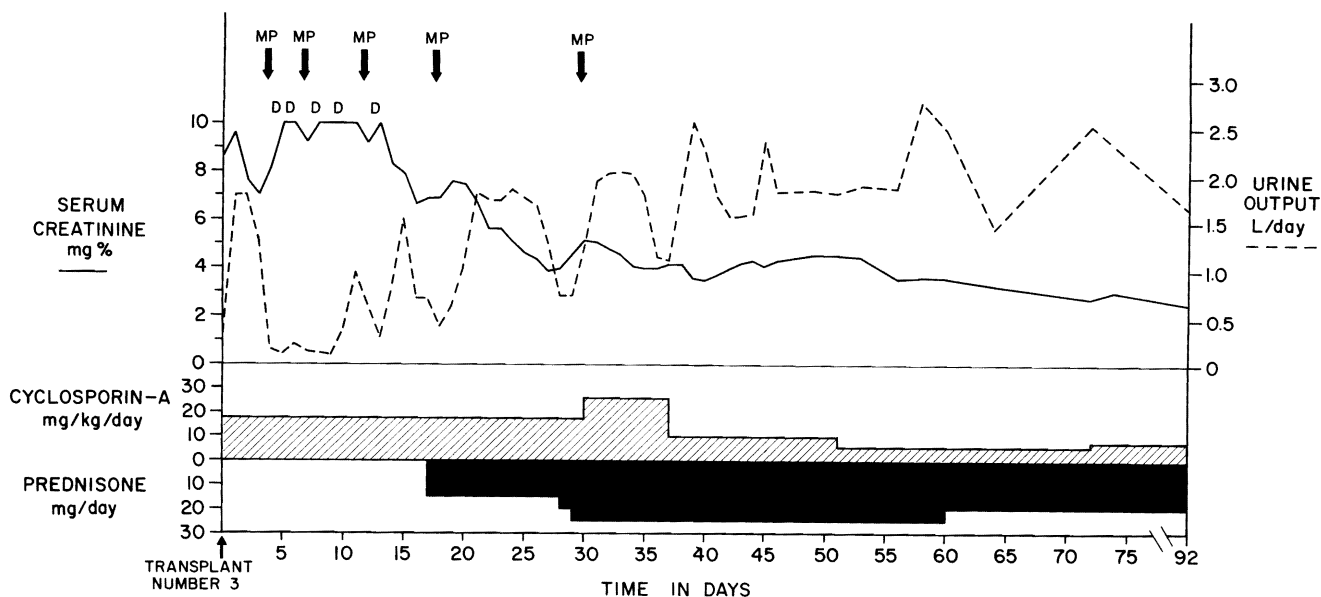
Fig. 2. The course of Patient 5 whose first cadaveric transplant in 1977 was rejected after 21 days. A second transplant was also rejected with azathioprine and prednisone therapy despite 30 days pretreatment with thoracic duct drainage. A third transplant was performed 50 days after the unsuccessful second transplantation. The patient was switched from azathioprine to cyclosporin A at that time, prednisone was stopped and thoracic duct drainage was discontinued two days later after a total of 82 days. See text for discussion. *D*, Dialysis; *MP*, methylprednisolone, 1 gram intravenously.

cortisone was followed with a short course of prednisone given orally, beginning at 200 or 160 milligrams per day and reducing this by 40 milligrams per day until 40 milligrams were reached. On the succeeding one or two days, the amount of prednisone was further reduced to a maintenance level of 10 to 20 milligrams per day, as shown in Figure 3.

Rejection Versus Nephrotoxicity

Response to therapy was the main determinant in making this distinction. When failing renal function, wound tenderness, graft enlargement and fever or various combinations of these findings were quickly ameliorated in the early postoperative period by steroid therapy, the patient was considered to have had an acute rejection. If imperfect renal function weeks or months after transplantation was promptly improved by the institution of steroid therapy, indolent rejection was judged to have been present.

Major changes in the cyclosporin A dosages were also made for combined diagnostic and therapeutic purposes. Occasionally, cyclosporin A was increased from the starting daily dose of 17.5 to 25 milligrams per kilogram. More commonly, the daily dose was reduced to 10 milligrams per kilogram or less. If the latter change resulted in improved renal function, it was considered that nephrotoxicity had been present.

Such drug manipulation for diagnosis was meaningful only when all treatment factors except one were kept stable. Thus, the cyclosporin A dosages were fixed during times of steroid change, and conversely, the steroid dosages were not altered during times of cyclosporin A adjustment.

RESULTS

Patient Survival

One of the 22 recipients died within the first two to four and one-half months. This patient was a 45 year old man who died five weeks after primary cadaveric transplantation. Definite kidney rejection never occurred, and the highest daily dose of prednisone after transplantation was 15 milligrams. Four days before death, a triple coronary artery bypass was performed to relieve cardiac symptoms which had predated transplantation but which had been misinterpreted at the earlier time. Re-exploration was required because of intrathoracic hemorrhage. After this, hypotension and heart failure became irreversible. Permission for performing an autopsy was denied.

Insofar as could be determined, cyclosporin A did not contribute to the death. Platelet counts and other coagulation measurements were normal prior to the revascularization of the coronary arteries.
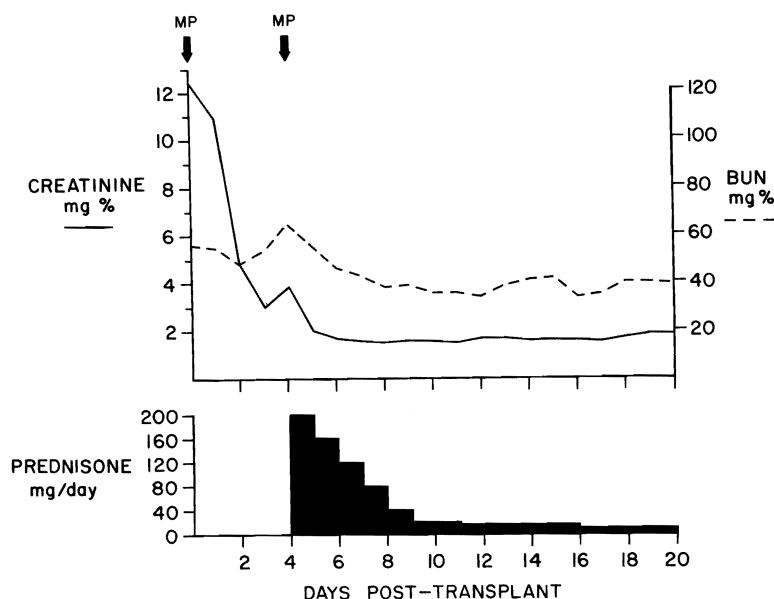
FIG. 3. Use of a short course of orally administered prednisone leading within five to seven days to maintenance therapy with 10 to 20 milligrams per day. This use of prednisone has been referred to as minicycle therapy. The daily dose of cyclosporin A was always 17.5 milligrams per kilogram.

Kidney Survival

In addition to the renal graft in the patient who died, two other kidneys were lost. Both were in patients undergoing retransplantation six to 18 months after rejection of the primary grafts. One of the recipients who was pretreated for 24 days with thoracic duct drainage was given a kidney that developed complete ureteral necrosis. After three unsuccessful attempts at reconstruction, the grossly normal organ was removed 16 days after transplantation. Thoracic duct drainage as well as cyclosporin A was continued for another 60 days when a repeat transplantation was successfully performed. The latest graft has not been considered in the results. Histopathologically, the graft which was excised after 16 days had relatively few abnormalities. There were scattered, small groups of infiltrating mononuclear cells in the interstitium. Similar cells were present in some of the peritubular capillaries. Less than 5 per cent of the mononuclear cells were lymphoblasts. The arterioles and arteries were normal. A few of the superficial cortical glomeruli contained increased amounts of mesangial matrix.

The third graft loss was in a 27 year old woman who earlier had rejected a kidney from a perfectly matched sibling donor. The cadaveric kidney transplanted with cyclosporin A treatment became oliguric within a few days. The patient had steroid, as well as cyclosporin A, therapy stopped after 44 days because a bleeding gastric ulcer developed. The homograft was removed two days later. The kidney was somewhat edematous, but it was pink, uniformly vascularized and not obviously rejected by gross criteria.

Histopathologically, there was evidence of cell mediated rejection as well as humoral rejection. The interstitium of the transplant contained many scattered, small to medium sized groups of infiltrating mononuclear cells. Similar cells were present in most of the peritubular capillaries. About 20 per cent of these infiltrating cells were lymphoblasts. Some of the intralobular and arcuate arteries were narrowed by intimal thickening associated with rupture of the internal elastic lamina. A few arteries were completely occluded. Ischemic changes were present in 15 per cent of the glomeruli, and 1 per cent were end-stage sclerotic.

Nineteen of the 22 original homografts treated with cyclosporin A are life-supporting. The function after two to four and one-half months is indicated in Table I.

Among the 18 primary cadaveric grafts, the only loss was by the patient death, leaving 17 of these primary cadaveric organs still working. The other two graft losses were among the four grafts used for retransplantation.

Early Rejection

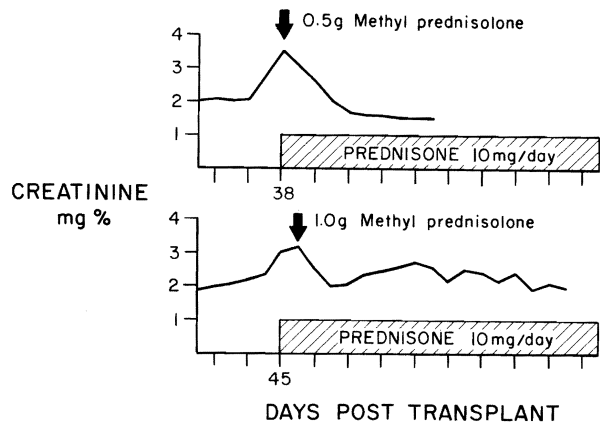All 22 of the cadaveric kidneys had prompt diuresis. Function thereafter was highly variable.

FIG. 4. Courses of Patient 3, top, and Patient 2, bottom, show acute rejection 38 and 45 days, respectively, after transplantation. No significant changes in urine output, body weight or temperature were recorded. Doses of cyclosporin A were 17.5 milligrams per kilogram per day throughout. Renal scans always revealed good flow, but there was decreased Hippuran, sodium *o*-iodohippurate, clearance before, during and after the aforementioned episodes. Note the declines in creatinine level after institution of low dosages of prednisone.

Fifteen of the 22 patients subsequently had what was diagnosed as definite acute rejection, most commonly occurring within the first week. One other recipient may have had early rejection, but the findings were equivocal.

The features of rejection that occurred within the first week (Fig. 1) often included oliguria, wound tenderness, graft swelling, fever and profound fatigue in addition to secondary increases of serum creatinine concentration and the blood urea nitrogen value. Not all elements of the syndrome were present in every patient, but those which were proved remarkably susceptible to steroid therapy. The systemic complications of fever and malaise could be relieved with as little as 100 milligrams of hydrocortisone, although 1,000 milligrams of hydrocortisone or, alternatively, 1,000 milligrams of methylprednisolone usually were given (Fig. 1). In most instances, this minimal adjuvant treatment either improved or stabilized renal function.

Rejection with the use of cyclosporin A did not proceed to graft necrosis, even when, in retrospect, the steroid therapy was suboptimal. The patient whose course is shown in Figure 2 frequently responded with a transient increase of urine output after a 1 gram bolus of intravenously administered methylprednisolone, but consistent life-supporting renal function was not obtained until maintenance therapy was begun with 30 milligrams per day of prednisone. In spite of the two and one-half week delay in providing appro-

priate maintenance steroids, a satisfactory result was eventually obtained.

A possible explanation for the dogged viability of rejecting homografts was observed in radionuclide scans. A typical finding was maintenance of good homograft blood flow but with poor excretion. Rarely seen were the declines in homograft blood flow which have been empirically associated with rejection by Stables and co-authors (18) and other authorities under conditions of conventional immunosuppression.

As it became obvious that rejection was a frequent problem in the early postoperative period, the burst of oral prednisone therapy added to the intravenous pulse therapy (Fig. 3) provided better immunologic control and a reduced necessity postoperatively for temporary hemodialysis. Thus, five of the first 13 patients had to be supported with dialysis after undergoing transplantation compared with only one of the last nine patients.

Late Rejection

Four patients who were discharged from the hospital receiving therapy with cyclosporin A alone, and three more, who had low dose steroid therapy as well, had slow, subsequent deterioration of renal function. Graft function became better when prednisone was begun or was increased from the preceding level (Fig. 4). Because of the steroid responsiveness, it was concluded that delayed rejection had occurred.

Nephrotoxicity

Because of the high incidence of significant albeit highly treatable rejection, an effort was made to maintain the dose of cyclosporin A at the high level of about 17.5 milligrams per kilogram per day for at least the first two postoperative months, even if nephrotoxicity was suspected. If a reduction in the dosage of cyclosporin A was followed by an improvement in renal function, it was concluded that nephrotoxicity had been responsible for the graft dysfunction. This chain of events was observed in seven of the 22 patients (Fig. 5) who are identified in Table I as Patients 3, 4, 5, 11, 13, 21 and 22.

Pretreatment, Eventual Function and Steroids

The renal graft function and steroid treatment in each patient after two to four and one-half months are summarized in Table I. By clinical assessment, the best results occurred in the 11 patients who had preoperative conditioning by lymphoid depletion. The only kidney loss was from
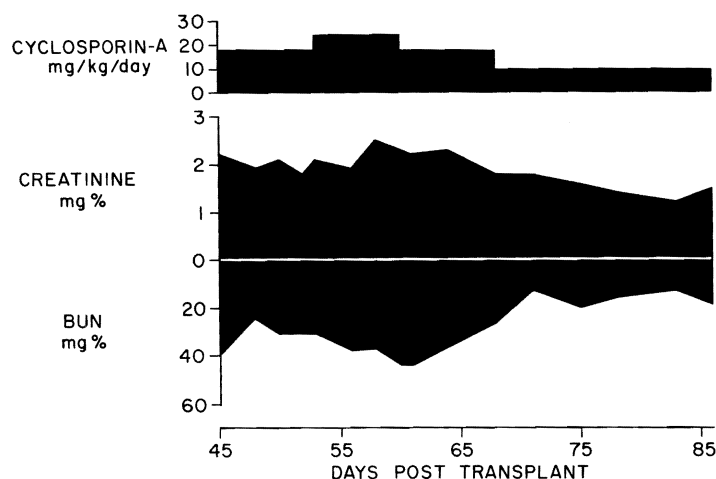
FIG. 5. An example of cyclosporin A nephrotoxicity is shown in the course of Patient 4. The cyclosporin A dosage was at first increased with resulting rises in the creatinine and blood urea nitrogen levels. Note that both measures returned toward normal within a few days after reducing cyclosporin A dose to 9 milligrams per kilogram per day. The prednisone dose was kept at 15 milligrams per day throughout the time shown.

homograft ureteral necrosis in a recipient who was given a successful subsequent transplant. Rejection usually was not severe in the patients prepared by lymphoid depletion, and early steroid requirements were minimal.

However, the results were also excellent in the 11 patients who did not have lymphoid depletion but who were pretreated for one to 18 days with cyclosporin A. There was no obvious difference in patients pretreated with cyclosporin A for a brief, as opposed to a longer, time (Table I). Although there was one death among the 11 patients not prepared by lymphoid depletion, the mortality was not related to the transplantation. One graft was lost to rejection.

Extrarenal Toxicity of Cyclosporin A

Cyclosporin A was well tolerated orally. Many patients had a flushing sensation of the abdomen, face, neck or total body within an hour after ingesting the drug. Examples were also seen of the minor hirsutism, gum hyperplasia and tremor that have been described by Calne (5, 6) and Powles (16) and their associates. There were no examples of leukopenia or other evidence of bone marrow depression.

In six of the 22 recipients, hepatic dysfunction developed with the use of cyclosporin A, always when the high daily dose of about 17.5 milligrams per kilogram was being given (Table I). All six of the patients became chemically jaundiced with peak serum bilirubin levels of 1.9 to 6.6 milligrams per cent. There were also increases in serum transaminase and alkaline phosphatase values and prothrombin times, but the patients were asymptomatic. When the daily dose of cyclosporin A was reduced to 10 milligrams per kilogram or less, the liver function abnormalities regressed. Two of the 22 patients who were known HB$_s$Ag carriers and who were suspected of having chronic aggressive hepatitis did not have hepatic complications with cyclosporin A therapy. These were Patients 1 and 17 as described in Table I.

No lymphomas or other malignant tumors were observed. There were three significant infections, of which at least two and possibly all three preceded cyclosporin A treatment. In one patient, nocardia infection developed in the lung which was treated with erythromycin and ampicillin. Another recipient with probable activation of colonic amebiasis was treated with metronidazole. A third patient with pleural granulomas and possibly active tuberculosis is undergoing treatment with isoniazid, rifampin and ethambutol.

DISCUSSION

The exceptional effectiveness and safety of cyclosporin A were evident throughout these early trials. The only death among the first 22 cadaveric kidney recipients was from a cardiac surgical complication that seemingly had no relation to the renal transplantation. There have been no other life-threatening complications in the follow-up periods of two to four and one-half months.

All but three of the original 22 transplants are functioning well, and in one patient, whose original graft had ureteral necrosis, a second organ was provided a few weeks later. Thus, all but two of the 22 recipients have been liberated from dialysis. Seventeen grafts survived in the 18 patients receiving kidney transplants for the first time, the only loss being from the cardiac surgical death.

Such a high rate of success was not attributable to cyclosporin A alone. As was the case with azathioprine nearly 20 years ago (19, 21), steroid therapy provided the means for rapid adjustments in immunosuppression, especially in the first postoperative days and also subsequently in patients whose renal function was subnormal after one or two months. The difference from past experience with conventional immunosuppression was that with cyclosporin A, the steroid component of combined immunosuppression was only a small fraction of that required in the past to achieve inferior results at considerable risk to life.

The divergence of our views from those of Calne and co-authors (5, 6, 8) concerning the role and value of steroid therapy hinges on the question of whether episodes of sudden postoperative renal failure have been due to rejection or to cyclosporin A nephrotoxicity. The paucity of histopathologic findings in graft biopsies convinced Calne and associates (5, 6, 8) that rejection was not the explanation. If biopsies of the kidneys had been obtained in our recipients, there is no reason to believe that major stigmas of rejection would have been different from the samples of Calne and colleagues (5, 6, 8). In the patients in our series with acute graft failure, radionuclide scans usually showed such good blood flow to the poorly excreting transplants that the most traditional diagnosis on strict but empirically derived radiologic criteria would have been acute tubular necrosis.

Yet, the therapeutic response to prednisone or even to hydrocortisone was so dramatic as to leave little doubt about an immunologic component of these crises. In patients in whom the grafts deteriorated at a later time, the improvement of renal function that followed the institution of as little as 10 milligrams per day of prednisone was equally convincing.

Nevertheless, a background role of drug toxicity may have been contributory. An argument could be mounted that the clinical manifestations of histopathologically and hemodynamically minor rejections were amplified by underlying cyclosporin A nephrotoxicity of the kind seen by Powles and co-workers (16) in their bone marrow transplant recipients. There were seven examples in our experience of moderately impaired renal function which five weeks to three months after transplantation returned toward normal when the daily dosage of cyclosporin A was abruptly reduced. Clearly, some such experimentation may be necessary in individual patients to arrive at a differential diagnosis between rejection and nephrotoxicity.

With the combination of cyclosporin A and prednisone, it will be desirable to minimize the moment to moment judgments that have dictated the timing and extent of the steroid treatment. Now that it is known that prednisone usually will be required for cadaveric kidney recipients in addition to cyclosporin A, we plan in some, and possibly most, future patients to provide a five or six day burst of steroid therapy similar to that shown in Figure 3, but beginning on the day of transplantation and ending with a small daily maintenance dose of 10 or 20 milligrams. The rationale for this use of steroids is analogous to that advanced many years ago for the prophylactic administration of prednisone with azathioprine (19).

As clinical trials with cyclosporin A expand, flexibility of planning and purpose will be important. Randomized trials have been proposed comparing cyclosporin A alone with conventional treatment by azathioprine and prednisone. Yet, our experience herein reported suggests that the use of cyclosporin A as the sole treatment would be suboptimal. More pilot studies seem necessary with combination therapy, but if the results remain as good as they have been in our trial, and with as much freedom from chronic steroid morbidity, it will be difficult within the limits of informed consent to find control patients to undergo so-called conventional treatment with azathioprine and prednisone (19, 21) or azathioprine, prednisone and antilymphocyte globulin (20).

An admonition not to begin randomized trials with cyclosporin A before learning how to use the drug properly would have seemed foolish a few years ago before the reflex acceptance of all such trials. However, as the clinical application of cyclosporin A widens, there will be questions, such as the prophylactic administration of steroids, that will be susceptible to investigation by randomization. Inquiries about recipient pretreatment also will be important. The value of pretreatment has been emphasized by our own studies of thoracic duct drainage (22). In an application of the pretreatment principle delineated

by that experience, half of the patients in the series herein reported were prepared for transplantation by thoracic duct drainage or lymphapheresis to which the first dosage of cyclosporin A was added a few hours preoperatively. The other 11 patients were preconditioned instead with cyclosporin A for one to 17 days. There were no striking differences in the results between the two groups. It is not even certain if either pretreatment technique was better than if cyclosporin A had been instituted on the day of transplantation with no prior therapy.

Of far greater importance than defining the preoperative value of cyclosporin A will be delineation of its chronic postoperative use. So far, the use of cyclosporin A in the patients in our series has proved to be so safe that we plan to continue it indefinitely. There has been no bone marrow depression, little serious hepatotoxicity and few complaints about gum hyperplasia, hirsutism and tremors. No new tumors have been seen, such as described by Calne and associates (5) in humans and by Bieber and colleagues (1) in subhuman primates. Within the 34 patients treated by Calne and collaborators (5), the 23 bone marrow recipients reported by Powles and co-authors (16) and the 22 patients of the present series, there were three lymphomas for a *de novo* tumor incidence of 3.8 per cent. Both the frequency of new tumors and the disproportionate number of lymphomas have been comparable with those in our kidney recipients (20) and those reported by Penn (14) who were treated with azathioprine and prednisone with or without antilymphocyte globulin.

SUMMARY

Eighteen patients were treated with primary cadaveric renal transplantation using cyclosporin A therapy, and four more patients underwent cadaveric retransplantation. Eleven of the 22 recipients were conditioned with lymphoid depletion before transplantation, using thoracic duct drainage or lymphapheresis for two to eight and one-half weeks. Cyclosporin A was begun a few hours before grafting. The other 11 patients were pretreated with cyclosporin A for from one day to 18 days.

After transplantation, the majority of patients in both subgroups of 11 had rejection develop, but in most, the immunologic process was readily controlled with relatively small dosages of prednisone. After follow-up periods of two to four and one-half months, one patient has died of the complications of a coronary artery reconstruction that was not related to the transplantation. Another graft was lost from rejection, and a third organ was removed because of ureteral necrosis. Nineteen of the original 22 cadaveric kidneys are functioning, including 17 of the 18 kidneys given to patients who were undergoing transplantation for the first time. The only loss in the latter group of 18 patients was in the patient who died after an open heart operation.

Results of these studies have shown that cyclosporin A is a superior and safe immunosuppressive drug but that, for optimal use in cadaveric transplantation, it usually should not be given alone. Steroid therapy greatly amplified the value of cyclosporin A. Unless major delayed morbidity develops which is not obvious so far, this drug combination should permit revolutionary advances in the transplantation of all organs. Other adjuncts to the cyclosporin A-steroid combination, including lymphoid depletion techniques, will require further investigation.

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