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Morbidity, mortality, and graft function in renal transplant recipients : a comparison of the effects of cyclosporine versus azathioprine

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IN RENAL TRANSPLANT RECIPIENTS:
A COMPARISON OF THE EFFECTS OF
CYCLOSPORINE VERSUS AZATHIOPRINE



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Morbidity, Mortality, and Graft Function
in Renal Transplant Recipients:
A Comparison of the Effects of
Cyclosporine versus Azathioprine

A Thesis Submitted to the Yale University
School of Medicine in Partial Fulfillment
of the Requirements for the Degree of
Doctor of Medicine

by

Michael Scott Sherman

1986

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Acknowledgment

I would like to extend my deepest appreciation to my faculty mentor, Dr. Peggy Bia, whose advice and willingness to offer her time freely helped motivate me to complete this task. Her constant encouragement together with her contagious enthusiasm was a true inspiration.

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ABSTRACT

MORBIDITY, MORTALITY, AND GRAFT FUNCTION

IN RENAL TRANSPLANT RECIPIENTS:

A COMPARISON OF THE EFFECTS OF CYCLOSPORINE VERSUS AZATHIOPRINE

Michael Scott Sherman

1986

Some investigators have claimed that cyclosporine is a superior immunosuppressive agent compared to azathioprine. In order to evaluate this hypothesis in patients treated at Yale-New Haven Hospital, charts as well as inpatient and outpatient transplantation data sheets were reviewed for all patients who received kidney transplants between February 1983 and February 1985. There were 26 patients in the cyclosporine treatment group, 46 patients in the azathioprine treatment group, and 9 patients started on azathioprine but switched to cyclosporine within the first three months for intractable rejection. Morbidity, mortality, graft loss, number and severity of rejection episodes, and renal function, were compared in the renal transplant recipients treated with cyclosporine versus those given azathioprine. Analysis was also performed on the incidence of rejection in patients switched from cyclosporine to

azathioprine at three to ten months post transplantation as is the policy at Yale.

Analysis of the background characteristics revealed that the cyclosporine group differed from the azathioprine group in two areas: age and percent receiving cadaveric grafts. Patients treated with cyclosporine were significantly older than those immunosuppressed with azathioprine (44.0 ± 2.5 versus 31.6 ± 1.9 , $p < .001$). Also, the cyclosporine group had a higher percentage of cadaveric grafts implanted (100 percent versus 57.1 percent, $p < .0001$). Both of these differences arose because of the original policy in effect for cyclosporine use. Graft source, however, was controlled for in that comparisons between the two groups were performed for all patients and then repeated using only the subgroup of azathioprine treated patients who had received cadaveric grafts.

No difference between the groups was found for patient survival, graft survival, or overall patient morbidity (as measured by noting number of days hospitalized). These variables were compared at both six months and at one year. In addition, both groups were found to have experienced the same number of rejection episodes, again at both six months and at one year following transplantation. Although the total number of rejection episodes at one year was the same in both groups, the cyclosporine group experienced only half as many serious rejections (defined by the need for antithymocyte globulin or monoclonal antibodies or by graft loss) over this time period as had the azathioprine group (0.4 ± 0.1 versus 0.8 ± 0.1 , $p < .05$).

Furthermore, although the azathioprine group had more serious rejections, their mortality and graft survival was no worse than the cyclosporine group. This observation is believed to result from improved methods of dealing with serious rejection episodes that have not responded to intravenous steroids.

Based on comparison of serum creatinine values, both at three and at six months, renal function was found to be better in the azathioprine treated patients at three months ($1.50 \pm .10$ versus $2.12 \pm .15$ mg/dl, $p < .001$) although this disparity was no longer statistically significant at six months ($1.67 \pm .18$ versus $2.16 \pm .20$ mg/dl, $p > .05$). Moreover, the difference at three months was no longer evident once serum creatinine values were compared only for the cadaveric transplantation patients in each group ($1.71 \pm .19$ versus $2.12 \pm .15$, $p > .05$). Thus, it is likely that the overall azathioprine group had better renal function at three months than the cyclosporine group because it contained a greater number of living related transplant recipients rather than because of nephrotoxicity in the cyclosporine group. It is however unclear why this did not hold at six months.

Following a switch from cyclosporine to azathioprine, four of sixteen cyclosporine patients experienced rejection within three months. However, one episode occurred in a patient who had been switched eight weeks earlier and another in a person who had a viral illness at the time of switch and then rejected one week later. Thus, there are only two incidents of rejection (at two and four weeks) which appear to be clearly related to the withdrawal of cyclosporine. Although there is no control group

for these patients, even two rejections occurring within one month of being switched from cyclosporine to azathioprine seems to be a suspiciously high number in patients who were out more than six months from their transplant.

In summary, the current study demonstrated that cyclosporine was not found to confer any advantage with regard to either patient or graft survival. Nor did cyclosporine treated patients require less days of hospitalization post transplantation. However cyclosporine treated patients who did suffer rejection episodes had less severe ones. The lack of difference in graft survival between the two groups may be explained by the availability of more effective means of treating rejections in azathioprine patients, by the initial use of cyclosporine only in high risk patients, or by the small number of patients in each group.

Review of Literature

I. Historical Perspective

From the first crude attempts at immunosuppression a quarter of a century ago to the first clinical trial of cyclosporine in 1978, immunosuppression of renal allografts has come a long way and has been the subject of a great deal of research. In 1959, Schwartz and Damashed first demonstrated that 6-mercaptopurine (6-MP) had the ability to induce immunological tolerance in adult rabbits (1). In the following year, 6-MP was used in renal transplant experiments in dogs by Calne (2) and Zukoski and coworkers (3). Their efforts showed that albeit tolerance did not develop, graft survival was prolonged in some animals.

In 1961, azathioprine, an imidazolyl derivative of 6-MP, was first synthesized (4). Animal studies soon showed that azathioprine possessed less toxicity than 6-MP (5), and it was first used in a human renal transplant recipient in 1961 in Boston. In the first two patients, there was no evidence of increased survival with azathioprine; however, in the following year, the first extended success with transplanted kidneys was seen (6-7).

Many centers began to add steroids to their immunosuppressive regimens in 1962. Yet for several years, they were used only for rejection episodes (8). After reports by Starzl et al. (9) and Goodwin et al. (10), the use of both azathioprine and steroids together became a standard regimen; and even today, the combination - often referred to as conventional

immunosuppressive therapy - remains the standard to which all other regimens are compared.

Cyclosporine, formerly known as cyclosporin A, is a fungal polypeptide composed of eleven amino acids, one of which is unique; most are hydrophobic, making the drug soluble only in lipids or organic solvents. First isolated from soil samples by the microbiology department at Sandoz, it was shown by Jean Borel to have potent immunosuppressive activity in a variety of in vitro and in vivo situations (11-12). Some twenty years after azathioprine first came into clinical use, Calne introduced cyclosporine into clinical practice (13), and in 1978 the first clinical trial began in Cambridge (14).

II. Azathioprine

The imidazole derivative, azathioprine, interferes with blastogenesis (involving DNA and RNA synthesis), which is known to be involved in the immune response. This blastogenic response can be measured by a variety of radioactive labeling techniques and is an early event in T cell response. It is therefore believed that azathioprine exerts its major effect by preventing the expansion of T lymphocyte clones responding to foreign antigens. Moreover, azathioprine effects the inflammatory reaction as well as both cell-mediated and humoral immunity (15). In vitro, azathioprine is known to alter most T cell markers and functions. For example, studies show that it inhibits mixed lymphocyte reactions along with the subsequent generation of

cytotoxic T cells (16). Azathioprine has also been shown in laboratory studies to be particularly active against suppressor T cells (17), an effect also found in vivo in renal transplant recipients (18). As mentioned earlier, azathioprine is also active against B cells but less intensely than against T cells. For example, in one investigation, mouse T cell rosettes were inhibited by lower doses of the drug than those required for B cell rosette inhibition (19).

Investigators long ago confirmed that azathioprine prolongs the survival of transplanted kidneys and other organs (20-21). Today, one year mortality for renal transplant recipients treated with azathioprine is very low, especially at the major centers. For example, a recent review of the statistics for a large population of azathioprine treated patients revealed one year graft survival of 75 percent and patient survival of 95 percent for patients receiving grafts from living related donors; for persons receiving cadaveric kidneys, the results were 56 percent and 86 percent, respectively (22).

Although azathioprine is a valuable immunosuppressive agent, it does have a number of serious side effects, the most common of which is a dose-dependent bone marrow suppression which effects mainly the production of white blood cells; in contrast, platelet production is rarely affected. Effect on erythrocytes is unpredictable; when it does occur, the result is usually a normochromic, normocytic anemia. Alopecia is another common, albeit less serious, side effect. However it is often transient, improving with modification of the azathioprine dose (23).

Azathioprine has also been reported to cause hepatic dysfunction although rarely of a serious nature. However, while hepatic toxicity has clearly been established in experimental animals, it is not certain that it occurs in humans in the doses used in renal transplant recipients (24). One side effect of azathioprine that has been documented is its tendency to encourage the development of malignant tumors, either pre-existing or grafted with the organ. Penn, who has established the International Transplant Tumor Registry, has published reports indicating that the incidence of tumors is approximately one hundred times greater than in the general population for the same age range (25). Yet, it is believed that for the stable patient on long term maintenance therapy, reduction of the daily dose from about 2.0-2.5 mg/kg to 1.5-2.0 mg/kg is safe and is associated with a decrease in the occurrence of malignancy (26).

III. Steroids

The pharmacology of steroids is very complex. They affect the immune system in a number of ways, especially at high doses. In addition to an effect on T lymphocytes, there is also a powerful anti-inflammatory reaction. One recent study showed that in therapy of acute rejection with methylprednisolone, the clinical effect is readily apparent within one to two hours, which is too rapid to be completely explained by a true immunosuppressive effect (27). More specifically,

corticosteroids have been shown to directly inhibit T cell proliferation. High concentrations of corticosteroids lyse mouse T cells but not human T cells; nevertheless, T cell proliferation is inhibited in human tissue culture (28). Recent investigations suggest that steroids reverse in vivo rejection episodes by preventing the production of interleukin-2, thus robbing the T cells of an essential factor needed for proliferation (29). Steroids, however, do not act directly on the interleukin-2 producing T cell; rather, they inhibit production by preventing macrophages from releasing interleukin-1, thereby blocking interleukin-1 dependent release of interleukin-2 from activated T cells (30).

The utility of steroids in the treatment of rejection episodes was first demonstrated in the early 1960's (31-32). Since that time, they have seen frequent use in the prevention of chronic rejection and in the treatment of acute rejection crises. One group of investigators found that rejection crises recur in 30 percent of cases after steroids have been discontinued and also that almost one-third of all crises are initiated by lowering of the steroid dose (33). Clinically, a high azathioprine/low steroid regimen is believed to be the best option as it provides adequate immunosuppression while minimizing steroid related complications (26). Today, the predominant use of steroids is in maintenance protocols which also employ azathioprine or cyclosporine, or in higher doses to treat acute rejection (34).

With regard to toxicity, steroids can produce many

complications and are a major contributor to post-transplantation morbidity and mortality. The side effects of steroids include growth retardation, a reduced rate of wound healing, predisposition to osteoporosis, avascular necrosis, cataracts, diabetes, obesity, Cushingoid features, and a number of other, less common problems (26).

IV. Cyclosporine

The new immunosuppressive agent cyclosporine has shown great promise in a variety of organs in addition to the kidney. For example, it has been widely used to modify rejection in bone marrow transplantation (35). Cyclosporine has a high degree of specificity for T cells. Studies show that it inhibits T cell proliferation induced by T cell mitogens, but in contrast, the action against B lymphocytes is much less (36-38). Several groups of investigators have used monoclonal antibodies to monitor the T lymphocyte subpopulations of renal allograft recipients; such studies have suggested that cyclosporine causes a reduction in the ratio of helper-inducer T cells to cytotoxic-suppressor T cells (39-40). With regard to mechanism, a number of research efforts have shown that cyclosporine interferes with the production of lymphokines, especially interleukin-2, by the helper T cell. Furthermore, interleukin-1 production by the macrophage as well as interleukin-3 production (colony stimulating factor) are probably inhibited as well (41-43), although these are not believed to be as important as

the effect on interleukin-2. It is likely that combined cyclosporine and steroid therapy is so effective because both act on interleukin-2 although through different mechanisms. Whereas cyclosporine acts predominantly on helper T cells, corticosteroids prevent interleukin-1 release from accessory cells (34). It has also been shown that cyclosporine does not appear to influence the inflammatory granulation response in vivo; this is consistent with the clinical observation that patients treated with the drug exhibit normal wound healing (44). With regard to pharmacodynamics, dosage must be determined on an empirical basis because of the erratic absorption that is seen. There is, however, a rough correlation between plasma level and degree of suppression of rejection of renal allografts (45-46).

A great number of animal experiments have been performed with cyclosporine, documenting the extensive prolongation of graft survival made possible by the agent. That cyclosporine is a potent inhibitor of allograft rejection has been demonstrated for heart, kidney, and skin grafts in a variety of species (36, 47-51). These will not be reviewed in detail here. However, one interesting study showed that a marked synergism existed between cyclosporine and antilymphocyte serum; although this study was performed in rats, the authors suggest that their findings may be relevant in clinical practice (52). Since 1978, many clinical studies have been done. One recent investigation produced data showing that cyclosporine provides for excellent graft survival in those recipients who differed from living donors by one haplotype and in recipients who were considered highly reactive

by mixed lymphocyte reaction (53). A number of clinical trials have been performed comparing cyclosporine to conventional therapy; these are reviewed in the discussion.

Like other drugs used for immunosuppression, cyclosporine has a long list of side effects. This includes nephrotoxicity, hepatotoxicity, lymphomas, dermatologic disorders hirsutism, rashes, skin thickening, gastrointestinal disturbance (anorexia, nausea, failure to gain weight), neurological problems (tremor, malaise and depression, burning sensation in limbs), cardiovascular effects (hypertension, fluid retention), and dental changes (gingival hypertrophy) (23).

In renal transplant recipients, the nephrotoxicity can be worrisome. This effect has been shown to be dose-related and reversible if the cyclosporine is stopped. It was noted in the Oxford trial that when patients were converted to azathioprine and prednisolone at three months, they underwent a rapid and significant improvement in their renal function (46, 54). Bone marrow recipients have also exhibited a return to normal renal function upon discontinuation of cyclosporine (55). The nephrotoxicity of this drug was first suggested by Calne and colleagues after the completion of an early clinical trial (14). This led to the recommendation that it only be used in patients whose kidneys were already making urine following transplantation (56). Interestingly enough, prior to the first report of renal toxicity in humans, no mention of this had ever been reported, even in ischemic kidneys exposed to cyclosporine (57). However, more recent experimental studies in the rat have demonstrated

proximal tubular damage, especially in the thick descending limb of the loop of Henle (58); yet it should be appreciated that this research involved very large doses of cyclosporine - 50-100 mg/kg. The presence of worsened renal function seen after liver and bone marrow transplantation further illustrates that nephrotoxicity is a real side effect (59-64).

One of the greatest difficulties of using cyclosporine in renal transplantation is differentiating as to whether deteriorating renal function is secondary to acute rejection or stems from cyclosporine toxicity. This is made even more difficult since cyclosporine can suppress the obvious signs of rejection (fever, graft swelling, tenderness). While a renal biopsy may prove helpful, the cellular infiltrates that are commonly seen in the grafts of cyclosporine treated patients can be difficult to interpret. A suggestion made by one team of investigators is that given a creatinine of greater than 300 micromol/L, rejection should be assumed and therapy with methylprednisolone begun. If the problem really is rejection, then a marked fall in creatinine should be seen after the use of the intravenous steroids. If on the other hand, either the serum creatinine is less than 300 micromol/L or the patient fails to respond to the methylprednisolone, a diagnosis of nephrotoxicity is made (regardless of cyclosporine levels), and the dose is halved (65).

Another major side effect is the increased incidence of lymphoma. In one early study, a very high rate of occurrence was seen, with three of twenty-nine patients getting lymphomas (37).

Subsequent studies have suggested a lower rate of lymphoma occurrence though. In summary then, cyclosporine is a major new immunosuppressive agent which has received a great deal of attention in recent years. The many encouraging studies which have been performed suggest that cyclosporine may help produce dramatic increases in graft and patient survival, especially for transplanted organs other than kidneys, since the success rate for renal transplants is so high especially at some of the major centers that a statistically significant increase might be difficult to detect.

Introduction and Purpose

The recent approval of the new immunosuppressive agent, cyclosporine, for routine clinical usage has been predicted to have a major impact on the area of transplantation surgery. By allowing better control of graft rejection, its use has been shown to be associated with results far better than those seen with more conventional treatment for a number of transplantable organs. Thus, many centers which previously had been reluctant to perform heart or liver transplantation have now begun to undertake these procedures with renewed enthusiasm. With renal allografts as well, some investigators believe that graft recipients have experienced less frequent rejection with cyclosporine. At Yale-New Haven Hospital, for example, cyclosporine was first reserved for patients designated as being at increased risk of graft rejection. However in spite of the extremely high cost of the drug, just one year after its introduction, it had become the standard treatment for all patients receiving cadaveric kidneys.

Although many studies have recently appeared comparing the efficacy of cyclosporine to that of more traditional immunosuppressive regimens, there are still many questions remaining to be answered. By studying renal allograft recipients at Yale-New Haven Hospital, this investigation explores the following areas:

1. Comparison of morbidity and mortality in patients treated with cyclosporine versus those treated with azathioprine.
2. Comparison of number and severity of rejection episodes in the two groups.
3. Comparison of long term renal function in the two groups.
4. Evaluation of incidence of rejection in cyclosporine treated patients following replacement of cyclosporine by azathioprine after three to ten months as per Yale protocol.
5. Evaluation of graft survival, graft function, morbidity, and mortality in patients originally treated with azathioprine but later switched to cyclosporine because of intractable rejection.

Materials and Methods

To explore the effect of cyclosporine on morbidity, mortality, rejection, and graft function in renal transplant recipients, data was collected on patients receiving transplants at Yale-New Haven Hospital from February 1983 through February 1985. During the period studied, all transplants were performed by two transplantation surgeons, Dr. M. Wayne Flye (former Director of Organ Transplantation) and Dr. Martin Schiff (Department of Surgery - Section of Urology), thus eliminating one potential source of variability. Sources of information included patient charts, summary sheets containing relevant lab values and drug dosages during inpatient treatment, clinic records, and the personal files of Dr. Margaret Bia.

The patient population was broken down into three groups: a study group (N=26) consisting of patients receiving prednisone plus cyclosporine between December 1983 (when it first became available) and February 1985; a control group (N=49) consisting of patients who were transplanted between February 1983 and February 1985 and treated with prednisone plus azathioprine; and an "azathioprine failure" group (N=9) consisting of graft recipients who were originally begun on azathioprine but later switched to cyclosporine because of inadequate immunosuppression. Thus a total of 84 patients were studied. Most cadaveric patients were placed on cyclosporine once it became available.

In order to include as many high risk and cadaveric recipients in the azathioprine group as in the cyclosporine group, the period of analysis of azathioprine treated patients extended back to ten months before cyclosporine was introduced. The following convention is used throughout this study: Group C - cyclosporine (study) group, Group A - azathioprine (control) group, Group F - azathioprine failure group.

Although the azathioprine failure group is somewhat artificial in that it is the result of clinical decision rather than treatment protocol, these "crossover" patients are included for the sake of completeness since they were transplanted during the period of study. It is acknowledged that they do not represent current clinical practices (given that all cadaveric graft recipients are now receiving cyclosporine from the onset). Thus, whereas data from Groups C and A are directly compared using appropriate statistical tests, that of Group F is merely tabulated and presented.

Initially, between October 1983 and October 1984, only high risk patients were treated with cyclosporine. These patients were high risk in that they not only received cadaveric kidneys but also fulfilled one of the following criteria: age greater than 50, history of diabetes, prior failed transplant, or possessing greater than 50 percent HLA-directed antibodies prior to transplantation. Beginning in November 1984, the policy was altered to require that all cadaveric graft recipients be given cyclosporine. As previously explained, the reason that the azathioprine or control group includes those patients receiving

grafts during the ten month period prior to the introduction of cyclosporine is to help dilute the effect of having made the azathioprine treated cohort a "low risk" group by virtue of having selected out for cyclosporine treatment those patients most likely to encounter complications. Thus, an attempt was made to include a similar number of high risk patients in Group A as in group C.

One patient, who received a graft from her identical twin, is excluded from analysis as she received no immunosuppression. All patients received prednisone as part of their immunosuppressive regimen. The protocol for administration of immunosuppressive medications was as follows. Azathioprine was always given in the amount of 2 mg/kg beginning on the day of transplantation. Cyclosporine was given in quantities sufficient to maintain serum levels of 50-150 ng/ml by HPLC following an initial loading dose of either 15 mg/kg P.O. or 5 mg/kg I.V.. In all patients, prednisone was started at a dose of 2-4 mg/kg on the day of transplantation and tapered to .25-.40 mg/kg by the end of the first month.

Before undertaking an analysis of the data, it was first necessary to characterize the three cohorts. Thus, as part of a preliminary comparison, the following information was gathered on each patient: age, history of diabetes, source of kidney (cadaveric versus living related), number having lost a prior transplant, and degree of prior sensitization (measured as the percentage of HLA antigens against which antibodies were detected). Both peak and most recent values were recorded in the

assessment of prior sensitization. Note is made of diabetes as it is the main preexisting renal disease which has been found to be associated with increased patient morbidity after transplantation. With regard to results, the following information was collected. Data was gathered on occurrence of graft loss (as indicated by either nephrectomy or return to dialysis), number of days hospitalized, and number of rejection episodes. All were examined at both six months and one year after transplantation. Number of days hospitalized was tabulated in order to obtain a general indication of morbidity, as renal transplant patients are frequently hospitalized for reasons other than rejection (e.g. infections secondary to immunosuppression). Patient mortality at one year was also recorded and compared between groups. A review of the variables collected for each group and the comparisons made are listed in Table 1 (for groups A and C) and Table 2 (for group F). Furthermore, additional variables examined in group C alone are listed in Table 3. These tables also contain units of measure for the different variables.

It should be recognized that number of rejection episodes is necessarily greater than graft loss as many rejection episodes were satisfactorily treated and reversed. Rejection was recognized in the chart review by noting an intensification in immunosuppressive therapy (125-500 mg of methylprednisolone for 3-5 consecutive days, anti-thymocyte globulin, or monoclonal antibodies) along with a concomitant elevation in serum creatinine concentration. Most were confirmed by renal biopsy. Moreover, rejection events were further classified as to whether

they were severe. A severe episode was defined as one in which loss of graft occurred or anti-thymocyte globulin or monoclonal antibodies were required. A mild rejection was one treated only with pulse steroids.

Graft function was also compared between groups, by noting serum creatinine concentration at both three and six months post-transplant. Because this value was recorded to provide an indication of stable graft function at the times noted, patients in the midst of rejection episodes (at three or six months) had a creatinine value recorded that represented stable renal function following treatment for the rejection incident. Cyclosporine was frequently held initially in patients with primary graft non-function. Thus for individuals in the cyclosporine and azathioprine failure groups, record was made of the number of days elapsing between transplantation surgery and introduction of cyclosporine.

We also attempted to examine whether rejection occurred when cyclosporine treated patients were switched to azathioprine. Most cyclosporine treated patients had their immunosuppressive regimens modified sometime between the third and tenth month following transplantation since the Yale protocol calls for all cyclosporine treated renal transplant patients to be switched to azathioprine sometime during this time interval. Exceptions include patients experiencing chronic rejection, one patient who was found to be allergic to azathioprine, and one pediatric graft recipient, all of whom were continued on cyclosporine indefinitely. For those cyclosporine treated graft recipients

who were switched, the month at which this switch occurred was noted as well as the appearance and timing of any rejection episodes during the next three months.

With regard to data manipulation and analysis, all information was entered into an IBM 4381 mainframe computer and statistical tests carried out using the Statistical Analysis Systems (SAS) software package. The SAS variable names used to represent the different types of data collected are listed in Tables 1-3 (for use in reviewing the computer generated appendix). A summary of all collected data may be found in the appendix in Table A1.

Results

Analysis of Background Characteristics

In order to first obtain a picture of the different groups with respect to variables that might affect the results, factors such as age, source of graft, presence of diabetes, graft number, peak percent antibodies, and recent percent antibodies were compared. Table 4 contains a comparison of these background variables.

There were only two items which differed significantly between the cyclosporine and azathioprine treated patients: source of graft and age. 100 percent of the cyclosporine treated patients received cadaveric kidneys as compared to 57.1 percent of azathioprine treated patients ($p=.0001$). This is as expected as only recipients of cadaveric grafts were treated with cyclosporine during the period studied. Moreover, Group C patients were older than Group A patients: 44.0 ± 2.5 versus 31.6 ± 1.9 years ($p < .001$). A visual comparison of ages may be seen in figure 1. No significant differences were seen for graft number, meaning how many patients in each group were receiving their first, second, or third kidney transplant. Preformed antibodies to HLA antigens are thought by some to predict graft outcomes if the level is high. However, the peak percent antibodies as well as the most recent percent antibodies were similar in each group. There were also a similar number of diabetics in Groups A and C.

Table 5 lists background data for the azathioprine failures.

Not surprisingly, this group closely resembles Group A, whose patients were started and maintained on azathioprine. 67 percent of the Group F patients received cadaveric grafts, and the mean age was 32.6 ± 5.5 years.

Analysis of Morbidity, Mortality, and Graft Loss

Table 6 compares morbidity, mortality, and graft loss for Group C versus Group A, and Table 7 presents the same results for Group F. None of these indicators of outcome differed significantly between Groups C and A.

80.8 percent of the cyclosporine treated patients were alive at one year as compared with 91.8 percent of those treated with azathioprine. All of the azathioprine failures survived to one year. By six months, 19.2 percent of the cyclosporine treated patients had lost their grafts, while the figure was 24.5 percent for the azathioprine patients. Values for graft loss at one year are 26.9 percent and 26.5 percent respectively. These differences are not significant. 11.1 percent (1 of 9) of Group F experienced graft loss by six months; and in these patients, there was no further loss between six months and one year.

Overall morbidity was assessed by counting number of days hospitalized. During the first six months following transplantation, Group C patients spent an average of 49.0 ± 6.5 days hospitalized, while Group A patients spent an average of 39.2 ± 3.8 days as inpatients. Corresponding figures for the first year are 64.0 ± 13.0 days for Group C versus 44.0 ± 4.7 days for

Group A. Whereas cyclosporine treated patients tended to spend more time in the hospital, the differences were not significant at the .05 level. Group F tended to have the longest hospital stay of all, averaging 65.7 ± 4.7 days and 75.3 ± 5.7 days for six months and one year respectively. This is likely explained by the prolonged stay required to treat their multiple rejections. Figure 2 is a bar graph comparing the number of days hospitalized during the first six months for the three groups, and Figure 3 contains the same information for the first year.

Analysis of Rejection Episodes and Graft Function

Number and severity of rejection episodes were evaluated as was serum creatinine concentration. These findings are summarized in Table 8, which compares the data for Group A versus Group C and in Table 9, which summarizes the same information for Group F.

Cyclosporine treated patients experienced an average of $0.9 \pm .1$ rejections during the first six months and $1.1 \pm .2$ during the first year. Values for azathioprine treated patients are $1.0 \pm .1$ and $1.1 \pm .1$, respectively. These numbers are very close to one another, and indeed there are no statistically significant differences between the two groups, either at six months or at one year. These data are also presented in Tables 10 and 11, which tabulate the percentage of patients in each group with one, two, three, or four rejections at six months and at one year, respectively. These charts illustrate that at six months, 19.2

percent of cyclosporine treated patients had experienced more than one rejection episode versus 16.3 percent for the azathioprine treated patients. At one year, the respective values are a virtually identical 26.9 percent and 26.5 percent.

However, examination of the number of serious rejection episodes at one year reveals that cyclosporine treated patients experienced markedly fewer serious rejection episodes than did azathioprine treated patients. Group C patients had an average of $0.4 \pm .1$ serious rejection episodes each whereas for Group A patients, the value is $0.8 \pm .1$ ($p < .05$ by Student's t-test). Stated another way, no member of Group C had greater than 1 serious rejection episode, whereas 10.1 percent of Group A patients had such occurrences (Table 12). Group F patients experienced an average of $1.3 \pm .2$ serious rejections each, which is consistent with their eventually being switched to cyclosporine because of inadequate immunosuppression.

Graft function was assessed by recording serum creatinine concentration at both 3 and at 6 months. As seen on Table 8, at 3 months, the Group A patients had significantly better renal function than the Group C patients, with creatinine values of $1.50 \pm .10$ and $2.12 \pm .15$ mg/dl respectively ($p < .001$). By 6 months however, although azathioprine treated patients still tended to have lower serum creatinine concentrations than those subjects treated with cyclosporine ($1.67 \pm .18$ versus $2.16 \pm .20$ mg/dl), the difference was not statistically significant. This was not explained by switch to azathioprine in patients originally treated with cyclosporine since only three patients had been

switched by the six month mark. Group F patients were remarkably stable with regard to creatinine concentration, averaging $1.66 \pm .21$ mg/dl at 3 months and $1.67 \pm .25$ mg/dl at 6 months. Figures 4 and 5 are histograms illustrating serum creatinine concentration at 3 and at 6 months respectively for Group A; Figures 6 and 7 depict the same for Group C; and finally, histograms for Group F are shown in Figures 8 and 9.

Analysis of Results for Cadaveric Graft Recipients Only

Whereas all Group C patients received cadaveric grafts, only 57.1 percent of the Group A patients did. In order to control for this selection bias, the data was re-examined looking only at patients who had received cadaveric kidneys and the results tabulated.

Background comparisons for this subset of patients are listed in Table 13. As with the comparison for the entire group, the cyclosporine patients are significantly older: 44.0 ± 2.5 versus 34.1 ± 2.2 years ($p < .01$). However, now only 3.6 percent of the azathioprine treated patients are diabetic versus 23.1 percent of the cyclosporine treated patients ($p < .05$). There remains no difference with regard to graft number, peak percent antibodies, or recent percent antibodies.

Table 14 compares morbidity, mortality, and graft loss for cadaveric recipients in Group C versus Group A. There are still no significant differences for one year survival or number of days hospitalized, either at six months or at one year.

Comparing just cadaveric recipients, Group A cadaveric recipients tended to have higher graft loss than cyclosporine treated patients (39.5 percent for cyclosporine versus 19.9 percent for azathioprine) at six months and 39 percent versus 27 percent respectively at one year. These differences did not reach statistical significance.

Finally, number and severity of rejection episodes and serum creatinine concentration are compared for cadaveric graft recipients (Table 15). As before, there is no difference between the two groups with regard to total number of rejection episodes at both six months and at one year. However, cadaveric recipients in Group A still had a higher number of more serious rejections during the first year than did Group C patients ($1.0 \pm .1$ versus $0.4 \pm .1$; $p = .0001$). Although serum creatinine concentration tended to be higher in cyclosporine treated patients at either 3 months ($2.12 \pm .15$ mg/dl for Group C versus $1.71 \pm .19$ mg/dl for Group A) or at six months ($2.16 \pm .20$ mg/dl for Group C versus $1.73 \pm .19$ mg/dl for Group A); the differences are not statistically significant.

Analysis of Outcome for Cyclosporine Patients Switched to Azathioprine

Of 26 patients who were treated with cyclosporine, 16 were switched to azathioprine sometime between the third and tenth month. Of the remaining 10 patients, most lost their kidney or expired prior to being switched, while a few were kept on cyclosporine because of subacute or chronic rejection. Of those

16 who were switched, 4 (25%) suffered one rejection episode each over the next 3 months. Timing of the rejection episode for these four patients (relative to the switch) was as follows: 1 week (R.K.), 2 weeks (I.P.), 4 weeks (F.S.), and 8 weeks (R.B.). It should be noted however that the patient who had a rejection episode 1 week after being switched had an antecedant viral infection, and it cannot be determined whether the rejection was the result of the viral infection or whether it stemmed from the withdrawal of cyclosporine. Furthermore, it is not clear that the rejection that occurred in R.B. at eight weeks can be attributed to cyclosporine switch since the interval from switch to rejection was so long. Thus in only two patients (I.P., F.S.) can the rejection clearly be associated with a switch from cyclosporine.

Discussion

Background Characteristics

Direct comparison of cyclosporine and azathioprine treated patients was performed for all variables studied. Recognizing that azathioprine failures do exist, a separate group of such patients was evaluated but not compared directly to the other two because of its heterogeneity and the fact that it is the product of clinical decision rather than protocol. This study includes patients placed in the cyclosporine group because of the presence of one or more of the following high risk criteria: age greater than 50, history of diabetes, prior failed graft, or HLA antibodies greater than 50%; or, after November 1984, it included any recipient of a cadaveric graft. As mentioned in the materials and methods section, azathioprine treated patients from the ten month period prior to the introduction of cyclosporine were included in the study in an attempt to minimize the effect of having made the azathioprine cohort a low risk population.

For the most part, this strategy was successful. Comparison of the background characteristics reveals that the azathioprine and cyclosporine treated patients differed significantly in only two variables: source of graft and age. The former was unavoidable since no recipient of a living related donor kidney was given cyclosporine ($p < .0001$). The latter was significant at the $p < .001$ level with cyclosporine patients being older (44.0 ± 2.5

versus 31.6 ± 1.9 years). Both factors should be kept in mind in interpretation of the results. Graft number, recent and peak percent antibody, and the frequency of diabetes did not differ significantly.

Whereas it might have been helpful to control for the disparity in age by selecting a subset of younger cyclosporine treated patients for comparison with the azathioprine treated group, this was not possible as only 13 cyclosporine treated patients were less than 50 years of age.

Morbidity, Mortality, and Graft Loss

Patient mortality did not differ between azathioprine and cyclosporine treated individuals. Patient survival at one year was 80.8% for the cyclosporine treated patients and 91.8% for those on azathioprine. This difference did not prove to be statistically significant at the $p < .05$ level. These figures are low compared to published data (66), an observation believed to be attributable to the large number of high risk patients who received grafts at Yale. Even when only cadaveric graft recipients in the azathioprine group were compared to the cyclosporine cohort, there was still not a significant difference in patient survival (Table 14).

It is interesting to note that all azathioprine failures survived to one year. Since these patients were switched to cyclosporine because they had multiple rejections on azathioprine, they probably would have had less favorable results

than the azathioprine group had they remained in the that group and not been switched to cyclosporine.

Graft survival at six months was calculated and found to be 81.8 percent for cyclosporine versus 75.5 percent for azathioprine; at one year, graft survival was 74.1 percent and 74.5 percent respectively. Neither comparison was statistically significant. Moreover, a subgroup consisting of azathioprine treated cadaveric patients was compared to cadaveric patients given cyclosporine in order to control for graft source. Again the differences in graft survival were not significant at either six months or at one year. One year graft survival was 89 percent for recipients in Group F. This graft survival is quite good and appears to justify switching these patients from azathioprine to cyclosporine for unrelenting rejection episodes (Table 7).

As a general measure of morbidity, number of days hospitalized was determined at both six months and at one year. By six months after undergoing transplantation, patients in the cyclosporine group had spent an average of 49.0 ± 6.5 days hospitalized, versus 39.2 ± 3.8 days for those given azathioprine. At one year, the figures are 64.0 ± 13.0 and 44.0 ± 4.7 days for cyclosporine and azathioprine patients respectively. Although cyclosporine patients tended to spend a greater number of days hospitalized, the difference is not significant for either time interval (Table 6). Again, controlling for graft source by comparing only cadaveric graft recipients, differences in number of hospitalized days were still not significant (Table 14).

Number and Severity of Rejection Episodes

Number of rejection episodes was assessed at both six months and at one year. In addition, number of serious rejection episodes for the first year was compared, serious being defined as requiring therapy with either antilymphocyte serum or monoclonal antibodies, or resulting in graft loss. At six months 19.2 percent of the cyclosporine group and 16.3 percent of the azathioprine cohort had experienced two or more rejections (Table 10). This difference is not significant at the .05 level (Table 8). At one year, corresponding values were 26.9 percent and 26.5 percent for the cyclosporine and azathioprine groups respectively, also not significant (Table 11). Once again, analysis of the data was performed limiting the patients studied to recipients of cadaveric grafts in both groups. Yet again, differences failed to reach significance (Table 15).

Assessment of number of severe rejections during the first year revealed that cyclosporine treated patients had fewer serious rejection episodes than did those graft recipients on azathioprine (Table 12). In fact, cyclosporine patients averaged only half as many serious rejections ($0.4 \pm .1$ versus $0.8 \pm .1$, $p < .05$). Stated differently, no cyclosporine patient had more than one severe episode whereas 10.1% of those subjects treated with azathioprine had two or more such episodes. Similar results were demonstrated when the number of serious rejections were compared in just the cadaveric recipients of Group A versus Group

C (Table 15). Patients in the azathioprine failure cohort averaged $1.3 \pm .2$ serious rejection episodes during the first year. This is consistent with the fact that these patients were switched because of serious rejection. The high number of serious episodes in this group is noteworthy because, had these patients remained in the azathioprine group, they would have made that group appear even worse, hence accentuating a difference which is already statistically significant.

The Yale data concerning frequency and severity of rejections is consistent with the findings of the Minnesota group (67). Based on a study of cyclosporine versus standard immunosuppression, they showed that while cyclosporine does not decrease the incidence of rejection, the clinical features are often mild and one does not see the florid manifestations of acute rejection which occur in patients being treated with azathioprine.

Given that the azathioprine group had a larger number of severe rejections and the fact that serious occurrences require a prolonged course of antilymphocyte serum or monoclonal antibodies, one would expect that they would have accumulated a greater number of hospital days. However, comparison of number of days hospitalized revealed that there was no statistical difference between the two groups. It is known that other than rejection, the other major cause of morbidity in immunosuppressed transplant recipients is infectious disease. Considering that the cyclosporine patients are significantly older and hence at increased risk for infection by virtue of age (68), it seems

reasonable to hypothesize that cyclosporine patients spent as much time in the hospital as the azathioprine patients because of infections. Moreover, this is consistent with the evidence that cyclosporine is a more potent immunosuppressive agent than azathioprine. This hypothesis would require further analysis of the number of infections in each group for confirmation.

Given that the azathioprine group experienced more severe rejection, one might expect that these patient would have higher rates of graft loss as well as other measures of morbidity. Yet, as discussed earlier, such is not the case. Probably, the most plausible explanation stems from the great advances (especially with the availability of OKT3 monoclonal antibodies) made in the treatment of rejections. Thus, although the azathioprine patients had more severe rejections, the newer therapeutics used to treat rejection are so effective in reversing it that their outcome is no different from that of patients who have more mild rejection. Without the benefit of antilymphocyte serum or monoclonal antibodies, it is probable that cyclosporine treated patients would have had better results in terms of patient and graft survival. It is also possible that no difference in graft survival between groups was seen because of the small numbers in each group. In summary, while azathioprine and cyclosporine appear to have the same net effect on kidney survival, the severity of rejection is less in cyclosporine treated patients.

With regard to complications, there is some evidence that patients treated with cyclosporine are also more prone to lymphomas. This was first recognized shortly after cyclosporine

was first used in renal allograft recipients (69). With regard to the Yale population, only one of the 26 cyclosporine patients developed a lymphoma, which proved to be fatal; so it does not appear to have been a major cause of morbidity or mortality. There is also experimental evidence which supports the supposition that cyclosporine is associated with a higher incidence of lymphomas. One group showed that in the presence of cyclosporine, EBV infected B lymphocytes will proliferate unchecked because the T cell dependent control of this proliferation is inhibited (70).

Comparison with Other Clinical Trials

The Yale data do not support the concept that cyclosporine improves cadaveric graft survival. Other studies have reached conflicting conclusions. At this point, it is useful to briefly review the findings of some of the major clinical trials which have been performed. In one of the first clinical trials, Starzl and colleagues obtained very good results with cyclosporine, with one year graft survival of almost 80 percent (71). This study was uncontrolled and involved 66 consecutive recipients of 67 cadaveric renal allografts. Starzl attributed his results to the use of steroids as well as cyclosporine; however it should be appreciated that the steroid component was only a small fraction of that previously used with azathioprine.

Another early controlled trial, this one by Calne et al., also praised the efficacy of cyclosporine. They found that use

of cyclosporine was associated with an increase in one year actuarial graft survival from 50 - 55 percent to over 80 percent in recipients of cadaveric renal allografts (72). Furthermore 12 of 34 patients (35 percent) never required concurrent steroid therapy. On the other hand, in one of the first controlled clinical trials of cyclosporine versus azathioprine plus prednisone, Morris found that there was essentially no difference in graft survival at three months (38). There are two problems with this study: the small number of patients and the very limited follow-up.

Often quoted is a the long term retrospective analysis by Calne and colleagues, which compared cyclosporine to conventional therapy consisting of azathioprine plus prednisone. In this study, the cyclosporine patients did not receive steroids. They found that at four years after transplantation, there was no difference in terms of patient survival (86 percent for cyclosporine versus 76 percent for conventional therapy), graft survival (70 percent for cyclosporine versus 62 percent for conventional therapy), or incidence of rejection. While the cyclosporine patients did do slightly better, the differences were small and not statistically significant (73).

Another major study was the Canadian Multicenter Trial, in which cyclosporine plus prednisone were compared to the best available standard therapy. In this case however, while there was no significant difference in patient survival (96.6 percent for cyclosporine versus 86.4 percent for azathioprine), cyclosporine patients did do substantially better in terms of

graft survival (80.4 percent and 64.0 percent respectively). There was no difference in number of rejections (74). They conclude that cyclosporine is the drug of choice for maximizing graft survival in recipients of cadaveric renal allografts.

Another large study, the European Multicenter trial, published results similar to those of the Canadian study. They gave cyclosporine without steroids ("to avoid over-immunosuppression") and compared it with azathioprine plus steroids; only cadaveric graft recipients were studied. They found no difference in patient survival (94 percent for cyclosporine versus 92 percent for controls). For one year graft survival though, cyclosporine treated patients had significantly better results (72 percent versus 52 percent for controls). 24 of 84 patients were switched from cyclosporine to conventional therapy by the end of the first year. No comparison of incidence of rejection was included in this report (75).

A final clinical trial that will be summarized is that of the University of Minnesota group. They undertook a prospective randomized clinical trial in which cyclosporine plus prednisone was compared to standard therapy, the latter including antilymphocyte globulin as well as azathioprine plus prednisone. This study found that there was no difference in terms of graft survival at 22 months (83.5 percent with cyclosporine versus 82.3 percent for conventional therapy). If only cadaveric graft recipients were analyzed, there was still no difference in graft survival (84 percent with cyclosporine versus 80 percent for standard therapy). There was also no difference in patient

survival, with that figure being greater than 92 percent for all categories. They also did separate analyses focusing on source of graft and presence of diabetes and found that cyclosporine did not confer an advantage. They did however find that cyclosporine patients had a lower incidence of rejection episodes (67). Najarian and his colleagues attributed the lack of better results with cyclosporine to improved management with conventional therapy.

In summary then, while none of the four large trials summarized found that use of cyclosporine improved patient survival, two of the four concluded that it improved graft survival. In a brief summary of the major clinical trials, Evans gives several reasons for the mixed results. He points out that conventional therapy often varied from center to center as well as among centers within the same study. He also attributes the discrepancies to differences in cyclosporine protocols (both dosage schedules and variability of adjuvant steroids (31). One interesting point is that all of the centers publishing data generally have excellent transplantation surgeons and nephrologists.

Renal Function

As an indicator of graft function, serum creatinine concentrations were recorded at both three and at six months. Only stable values were used; patients in the midst of an acute rejection had their next stable creatinine value recorded

instead. It should be recognized that of 19 cyclosporine patients for whom six month creatinine values were available, only three had already been switched to azathioprine (all at about two months earlier). Thus, for the most part, the six month creatinine concentrations for the cyclosporine group may be said to accurately reflect function of kidneys exposed to cyclosporine.

At three months, cyclosporine treated patients had significantly worse renal function than did those subjects given azathioprine ($2.12 \pm .15$ mg/dl versus $1.50 \pm .10$ mg/dl, $p < .001$). By six months however, there was no longer any significant difference. If only cadaveric graft recipients are compared, then there is no difference at either point. This suggests that the cyclosporine group had higher creatinine values at three months because it possessed significantly more cadaveric grafts. However it is not clear then why there is no difference in function at six months. Since in the groups as a whole and in just the cadaveric recipients of each group, serum creatinine concentrations always tended to be higher in cyclosporine treated patients, it is possible that these differences would have reached statistical significance had larger numbers of patients been evaluated.

Other groups which have studied renal function in patients treated with cyclosporine have found similar results. Najarian et al. have published results which show a mean three month creatinine concentration of 1.98 mg/dl (s.d. $\pm .61$) and a mean six month creatinine concentration of 2.00 mg/dl (s.d. $\pm .52$) in

patients treated with cyclosporine (67). These values are very close to those of the Yale patients. Of note is the fact that this study excludes ten patients who were switched to alternate day cyclosporine after three months for nephrotoxicity. In the Canadian Multicenter Trial which studied cadaveric graft recipients only, cyclosporine patients were found to have significantly higher creatinine values at six weeks (2.6 mg/dl versus 2.0 mg/dl, $p=.03$) (74). A two year follow-up study which compared cyclosporine with azathioprine was published by the Cambridge group (23). Their data, which suggests that cyclosporine does not have a long term negative effect on renal function, is consistent with the Yale data. It should be appreciated that assessing the effect of cyclosporine on renal function can be difficult, even utilizing biopsies. For example, although it is known to be nephrotoxic, many of the morphological features of nephrotoxicity overlap with those of rejection. Separation of the two effects is not straightforward (23).

Post Cyclosporine Switch Data

Of the 26 patients in the cyclosporine group, 16 were switched over to azathioprine between three and ten months after undergoing transplantation as per protocol. Of the ten who were not switched, one was a pediatric patient (which are kept on cyclosporine indefinitely); a few were kept on cyclosporine because of chronic rejection; and the remainder either died or lost their grafts while still on cyclosporine. Of the 16 who

were changed over to azathioprine, four suffered rejection during the following three months: one each at one, two, four, and eight weeks after being switched. All of these patients were switched at either six or seven months after the original operation. Because one patient rejected eight weeks after being switched, it is not clear that his rejection may be directly attributed to the withdrawal of cyclosporine. In addition, the patient who suffered a rejection episode one week after being changed over to azathioprine had a viral infection, and it is unclear whether this rejection was set off by the viral infection or by the change in immunosuppressive regimen. Thus, only two (12.5 percent) of sixteen patients had rejections that were directly linked to the replacement of cyclosporine by azathioprine.

Given the lack of any type of control group as well as the small numbers involved, it is difficult to comment on the significance of this finding. However, for patients who received renal transplants at least six months earlier, even two rejections out of sixteen patients during a four week period seems to be rather high. Therefore, the only conclusion that can be drawn is that cyclosporine treated patients may have been at increased risk of rejection following the switch to azathioprine, but the relationship is far from clear.

In one animal study, dogs which had received cadaveric renal allografts were able to be converted from cyclosporine to azathioprine at three months without increased graft loss (76). However, the endpoint quoted in this study is graft loss not rejection, and results obtained in animals do not always extend

to humans. The Minnesota group has published results of a randomized clinical trial comparing cyclosporine versus azathioprine (67). They report on four patients who were switched from cyclosporine to azathioprine; of that number, one had an acute rejection episode within two weeks, while the others gradually improved. However, these four patients were switched because of cyclosporine-related nephrotoxicity rather than by protocol. Thus, this data cannot be directly compared to the Yale results. Finally, in one recent study, 14 renal transplant patients were switched from cyclosporine to azathioprine at three months. Of this number, eleven patients had no rejection episodes following the switch, while three patients suffered severe rejection leading to graft loss, all during the second week after switch (54). They conclude that there is an increased incidence of serious rejection after patients are switched. However, because two of the patients were already in midst of severe rejection crises at the time of switch, it is difficult to draw any firm conclusions from this report. Unfortunately, little has been published in this area, and much of what has been published is difficult to interpret, given the small numbers of patients and differences in reasons for switch; clearly, further research is needed in this area.

Summary

In summary, this study shows that at Yale-New Haven Hospital between February 1983 and February 1985, patient survival in

cyclosporine and azathioprine treated patients was similar. In addition, graft survival was similar for the two groups at six and at twelve months. Number of hospital days in each group was also similar. The number of rejections was similar but less severe with cyclosporine. Finally, renal function tended to be worse with cyclosporine but only reached statistical significance at three months.

Conclusion

Cyclosporine is a potent immunosuppressive agent. Although graft survival and number of rejection episodes are similar to conventional therapy, severity of rejections is improved. Further study is needed with more patients to determine whether cadaveric graft survival in renal transplant patients is consistently improved.

Table 1. Background Characteristics and Results
Compared in Group C Versus Group A

*

Background Characteristics

<u>Variable</u>	<u>Unit of Measure</u>	<u>SAS Name</u>
Source of Kidney	C=cadaveric L=living related	SOURCE
Age at Operation	years	AGE
Presence of Diabetes	Y=present N=not present	DIABETIC
Graft Number		GRAFT
Peak Percent Antibodies	percent	ABPEAK
Most Recent Percent Antibodies	percent	ABREC

Results

Mortality at 1 Year	A=alive D=dead	MORTAL
Graft Loss at 6 Months	Y=graft lost N=graft functioning	LOSS6MO
Graft Loss at 1 Year	Y=graft lost N=graft functioning	LOSS1YR
Period Hospitalized		
-During First Six Months	days	DAYS6MO
-During First Year	days	DAYS1YR
Rejection Episodes		
-During First Six Months		REJ6MO
-During First Year		REJ1YR
Serious Rejections		
-During First Year		REJSER
Creatinine at 3 Months	mg/dl	CREAT3MO
Creatinine at 6 Months	mg/dl	CREAT6MO

*Other data collected albeit not analyzed include Patient Initials (PT) and Transplant Date (TXDATE).

t-In tables and graphs prepared using the Statistical Analysis Systems software package, variables are referred to by these names.

Table 2. Background Characteristics and Results
Examined in Group F

* <u>Background Characteristics</u>		
<u>Variable</u>	<u>Unit of Measure</u>	<u>SAS Name</u> ^t
Source of Kidney	C=cadaveric L=living related	SOURCE
Age at Operation	years	AGE
Presence of Diabetes	Y=present N=not present	DIABETIC
Graft Number		GRAFT
Peak Percent Antibodies	percent	ABPEAK
Most Recent Percent Antibodies	percent	ABREC
<u>Results</u>		
Mortality at 1 Year	A=alive D=dead	MORTAL
Graft Loss at 6 Months	Y=graft lost N=graft functioning	LOSS6MO
Graft Loss at 1 Year	Y=graft lost N=graft functioning	LOSS1YR
Period Hospitalized		
-During First Six Months	days	DAYS6MO
-During First Year	days	DAYS1YR
Rejection Episodes		
-During First Six Months		REJ6MO
-During First Year		REJ1YR
Serious Rejections		
-During First Year		REJSER
Creatinine at 3 Months	mg/dl	CREAT3MO
Creatinine at 6 Months	mg/dl	CREAT6MO
Interval Between Transplant and Cyclosporine Introduction	days	PRECYC

*Other data collected albeit not analyzed include Patient Initials (PT) and Transplant Date (TXDATE).

t-In tables and graphs prepared using the Statistical Analysis Systems software package, variables are referred to by these names.

Table 3. Additional Results Examined in Group C

<u>Variable</u>	<u>Unit of Measure</u>	<u>SAS Name</u> *
Interval Between Transplant and Cyclosporine Introduction	days	PRECYC
Interval Between Transplant and Switch from Cyclosporine to Azathioprine	months	SWITCH
Number of Rejection Episodes within 3 Months of Switch		POSTREJ
Interval Between Cessation of Cyclosporine and Appearance of Rejection	weeks	TIMEREJ

*In tables and graphs prepared using the Statistical Analysis Systems software package, variables are referred to by these names.

Table 4. Comparison of Background Data
for Group C Versus Group A

<u>Variable</u>	<u>Group C</u>	<u>Group A</u>	<u>p value</u>
Number of Patients	26	49	
Percent Cadaveric	100%	57.1%	.0001 *
Age (years)	44.0 \pm 2.5	31.6 \pm 1.9	<.001 ^t
Graft Number	1.4 \pm .1	1.1 \pm .1	NS ^t
Percent Peak Antibody	21.0 \pm 5.3	9.5 \pm 3.3	NS ^t
Percent Recent Antibody	9.2 \pm 3.8	5.7 \pm 2.4	NS ^t
Percent Diabetic	23.1%	8.1%	NS *

Note: Standard Error of the Mean is given where appropriate.

* by Chi-Squared

t by Student's T-Test

Table 5. Summary of Background Data for Group F

<u>Variable</u>	<u>Group F</u>
Number of Patients	9
Percent Cadaveric	67%
Age (years)	32.6 \pm 5.5
Graft Number	1.0 \pm 0
Percent Peak Antibody	26.1 \pm 10.4
Percent Recent Antibody	18.7 \pm 11.4
Percent Diabetic	0%

Note: Standard Error of the Mean is given where appropriate.

Table 6. Comparison of Morbidity, Mortality, and Graft Loss
Results for Group C Versus Group A

<u>Variable</u>	<u>Group C</u>	<u>Group A</u>	<u>p value</u>
1 Year Patient Survival	80.8%	91.8%	NS *
Graft Loss at 6 Months	19.2%	24.5%	NS *
Graft Loss at 1 Year	26.9%	26.5%	NS t
Hospital Days - 6 Months	49.0 \pm 6.9	39.2 \pm 3.8	NS t
Hospital Days - 1 Year	64.0 \pm 13.0	44.0 \pm 4.7	NS

Note: Standard Error of the Mean is given where appropriate.

* by Chi-Squared

t by Student's T-Test

Table 7. Summary of Morbidity, Mortality, and Graft Loss
Results for Group F

<u>Variable</u>	<u>Group F</u>
1 Year Patient Survival	100%
Graft Loss at 6 Months	11.1%
Graft Loss at 1 Year	11.1%
Hospital Days - 6 Months	65.7±4.7
Hospital Days - 1 Year	75.3±5.7

Note: Standard Error of the Mean is given where appropriate.

Table 8. Comparison of Rejection Episodes and Graft Function Results for Group C Versus Group A

<u>Variable</u>	<u>Group C</u>	<u>Group A</u>	<u>p value</u>
Rejections - 6 Months	0.9 \pm .1	1.0 \pm .1	NS ^t
Rejections - 1 Year	1.1 \pm .2	1.1 \pm .1	NS ^t
Serious Rejections-1 Year	0.4 \pm .1	0.8 \pm .1	<.05 ^t
Creatinine - 3 Months (mg/dl)	2.12 \pm .15	1.50 \pm .10	<.001 ^t
Creatinine - 6 Months (mg/dl)	2.16 \pm .20	1.67 \pm .18	NS ^t

Note: Standard Error of the Mean is given where appropriate.

* by Chi-Squared

t by Student's T-Test

Table 9. Summary of Rejection Episodes and Graft Function Results for Group F

<u>Variable</u>	<u>Group F</u>
Rejections - 6 Months	1.4 \pm .2
Rejections - 1 Year	1.6 \pm .2
Serious Rejections-1 Year	1.3 \pm .2
Creatinine - 3 Months (mg/dl)	1.66 \pm .21
Creatinine - 6 Months (mg/dl)	1.67 \pm .25

Note: Standard Error of the Mean is given where appropriate.

Table 10. Frequency Distribution of Rejections in First Six Months

	Number of Rejections				
	0	1	2	3	4
Group A	20.41	63.27	12.24	2.04	2.04
Group C	26.92	53.85	19.23	0.00	0.00

The value in each cell is the percentage of patients in each group who had a given number of rejection episodes (ranging from 0 to 4) during the first six months.

Table 11. Frequency Distribution of Rejections in First Year

	Number of Rejections				
	0	1	2	3	4
Group A	20.41	53.06	22.45	2.04	2.04
Group C	23.08	50.00	23.08	3.85	0.00

The value in each cell is the percentage of patients in each group who had a given number of rejection episodes (ranging from 0 to 4) during the first year.

Table 12. Frequency Distribution of Serious Rejections in First Year

		Number of Serious Rejections			
		0	1	2	3
Group A		36.73	53.06	8.16	2.04
Group C		57.69	42.31	0.00	0.00

The value in each cell is the percentage of patients in each group who had a given number of serious rejection episodes (ranging from 0 to 3) during the first year.

Table 13. Comparison of Background Data for
Cadaveric Graft Recipients Only
 for Group C Versus Group A

<u>Variable</u>	<u>Group C</u>	<u>Group A</u>	<u>p value</u>
Age (years)	44.0 \pm 2.5	34.1 \pm 2.2	<.01 ^t
Graft Number	1.4 \pm .1	1.2 \pm .1	NS ^t
Percent Peak Antibody	21.0 \pm 5.3	12.7 \pm 4.3	NS ^t
Percent Recent Antibody	9.2 \pm 3.8	7.7 \pm 3.2	NS ^t
Percent Diabetic	23.1%	3.6%	<.05 [*]

Note: Standard Error of the Mean is given where appropriate.

* by Chi-Squared

t by Student's T-Test

Table 14. Comparison of Morbidity, Mortality, and Graft Loss
Results for Cadaveric Graft Recipients Only
 for Group C Versus Group A

<u>Variable</u>	<u>Group C</u>	<u>Group A</u>	<u>p value</u>
1 Year Patient Survival	80.8%	92.9%	NS *
Graft Loss at 6 Months	19.2%	39.3%	NS *
Graft Loss at 1 Year	26.9%	39.3%	NS t
Hospital Days - 6 Months	49.0 \pm 6.9	46.2 \pm 5.2	NS t
Hospital Days - 1 Year	64.0 \pm 13.0	49.6 \pm 6.0	NS

Note: Standard Error of the Mean is given where appropriate.

* by Chi-Squared

t by Student's T-Test

Table 15. Comparison of Rejection Episodes and Graft Function
Results for Cadaveric Graft Recipients Only
 for Group C Versus Group A

<u>Variable</u>	<u>Group C</u>	<u>Group A</u>	<u>p value</u>
Rejections - 6 Months	0.9 \pm .1	1.1 \pm .1	NS t
Rejections - 1 Year	1.1 \pm .2	1.3 \pm .1	NS t
Serious Rejections-1 Year	0.4 \pm .1	1.0 \pm .1	.0001 t
Creatinine - 3 Months (mg/dl)	2.12 \pm .15	1.71 \pm .19	NS t
Creatinine - 6 Months (mg/dl)	2.16 \pm .20	1.73 \pm .19	NS t

Note: Standard Error of the Mean is given where appropriate.

* by Chi-Squared

t by Student's T-Test

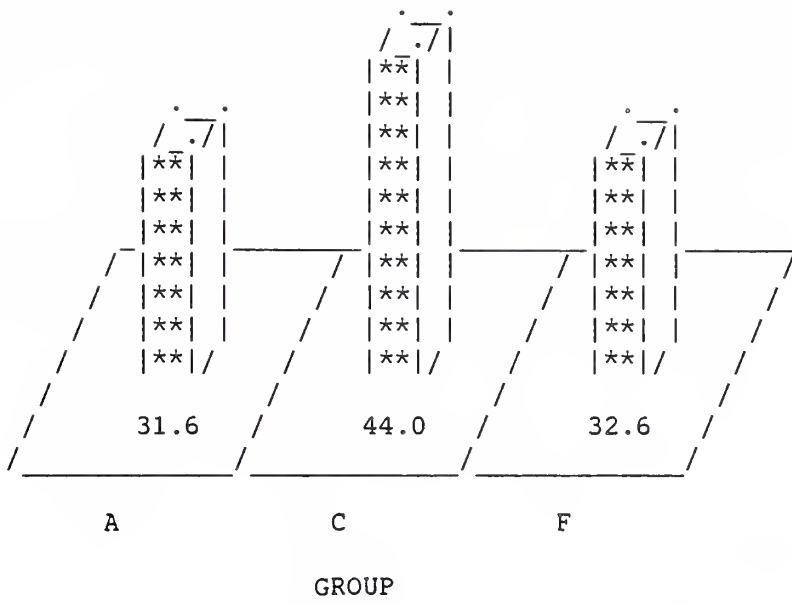
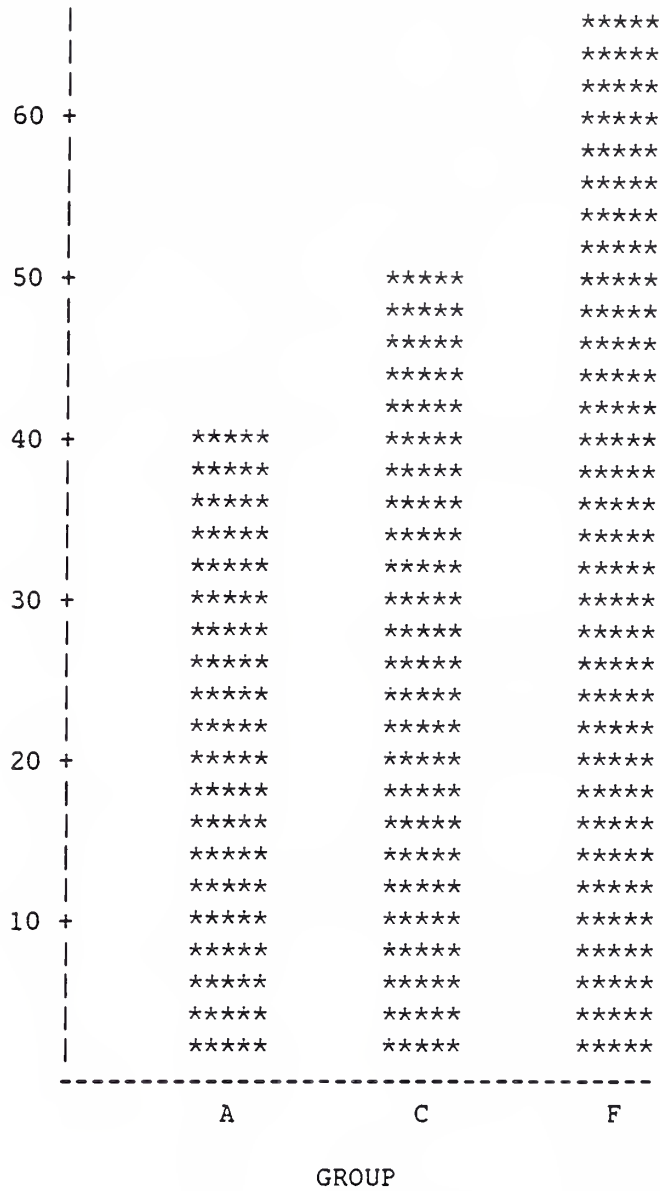


Figure 1. Comparison of Mean Ages of Study Groups

Standard errors of the mean are 1.9 for Group A, 2.5 for Group C, and 5.5 for Group F.



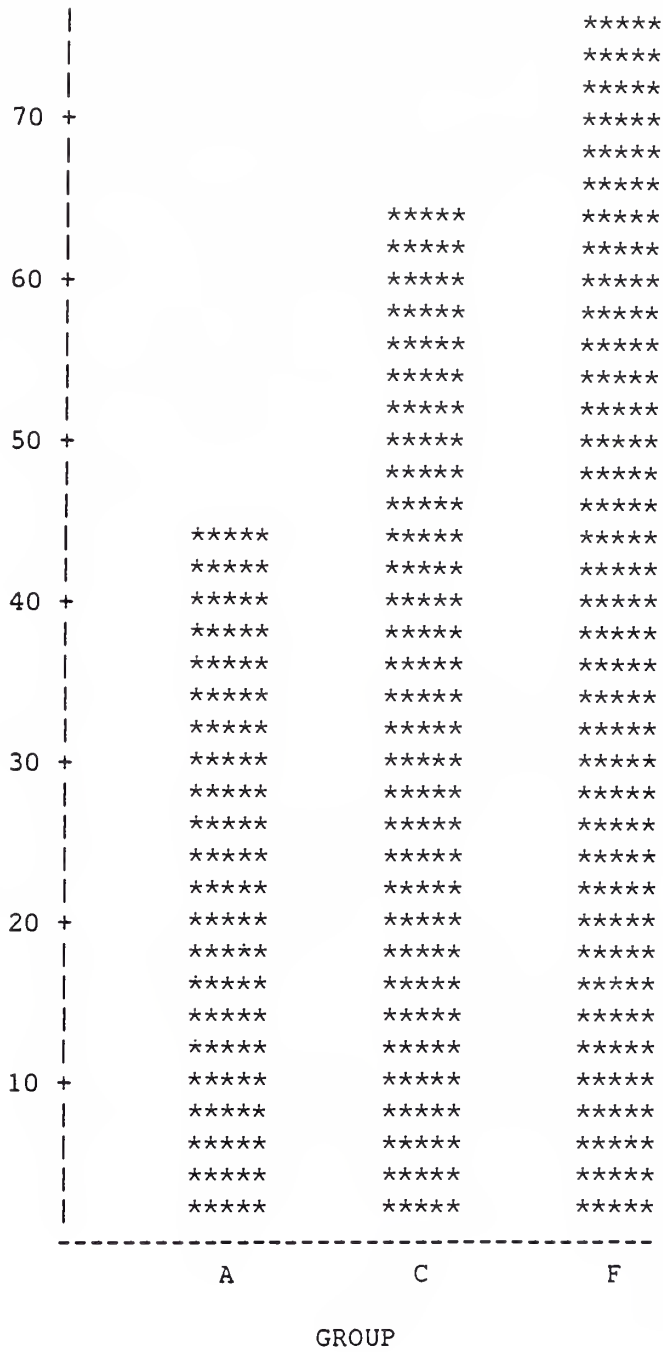
S.E.M. 3.8 6.9 4.7

Figure 2. Bar Graph Comparing Average Number of Days Hospitalized Over First Six Months

Note: The difference between Group A and Group C is not significant at the .05 level

DAYS

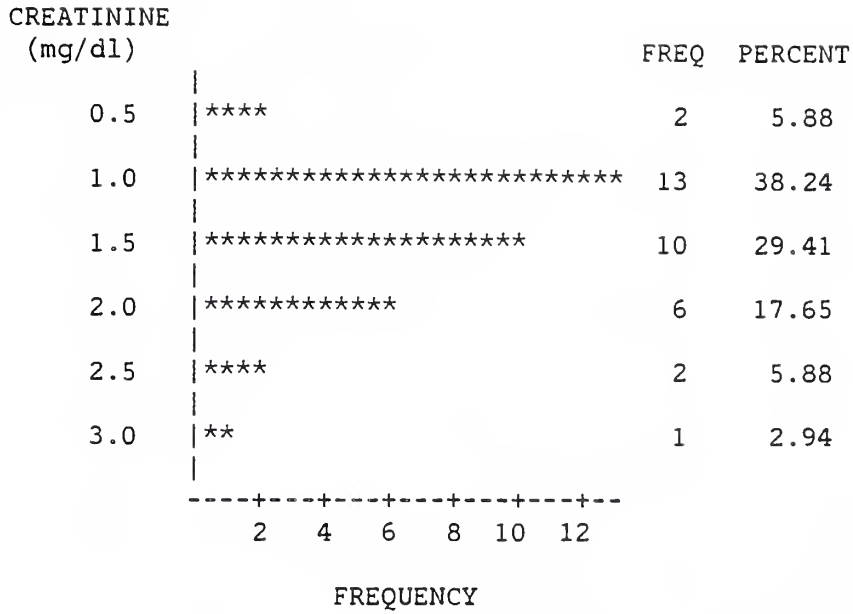
59



S.E.M. 4.7 13.0 5.7

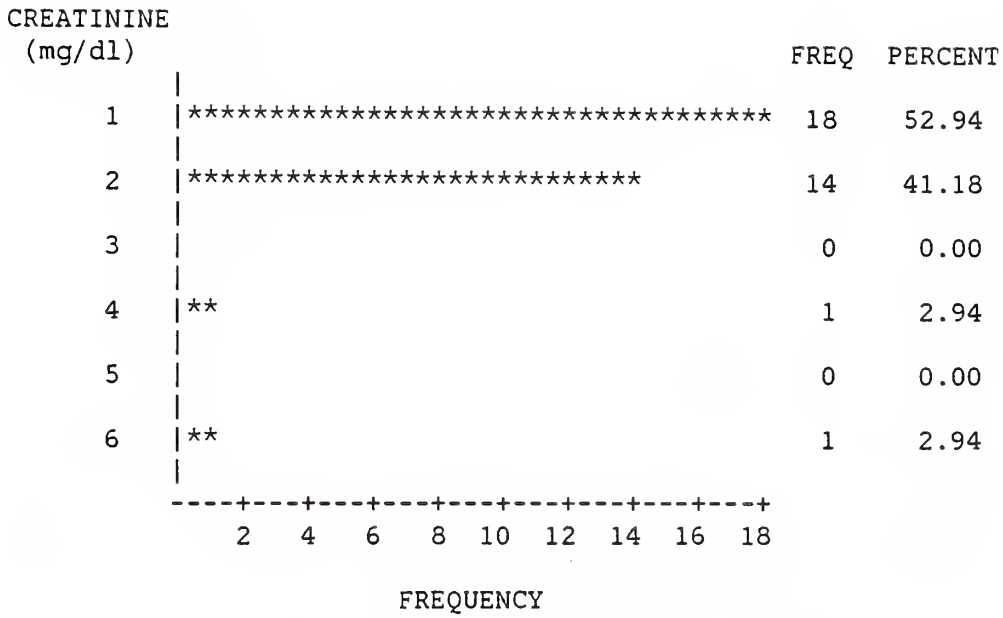
Figure 3. Bar graph Comparing Average Number of Days Hospitalized Over First Year

Note: The difference between Group A and Group C is not significant at the .05 level.



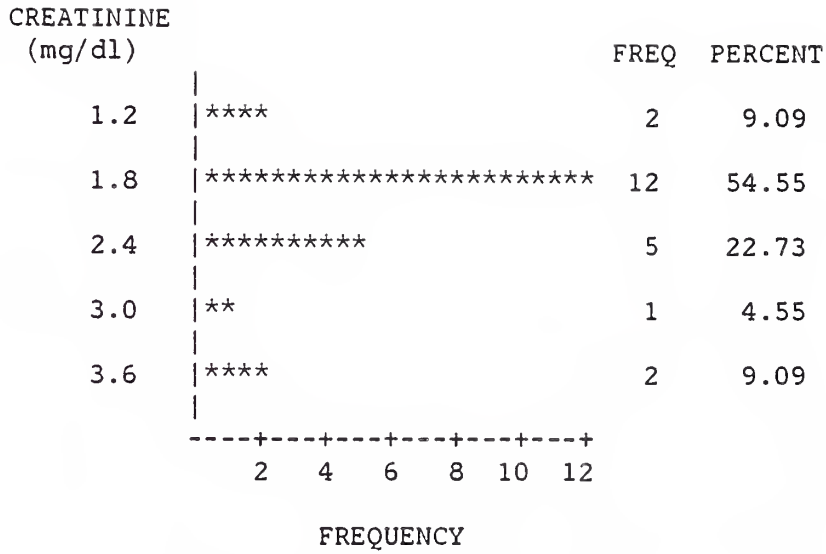
Mean=1.50
S.E.M.=.10

Figure 4. Histogram of Three Month Creatinine Values for Azathioprine Treated Patients



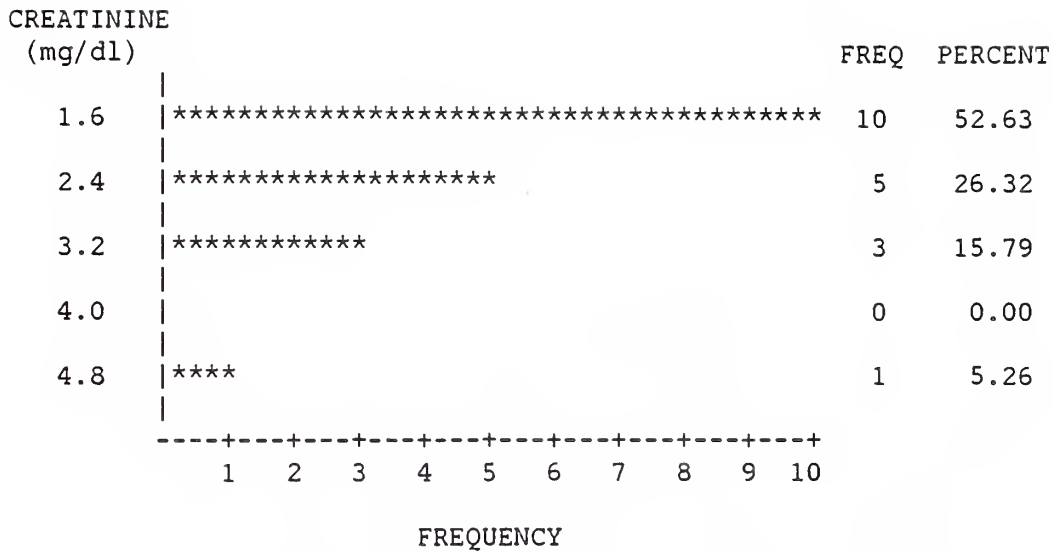
Mean=1.67
S.E.M.=.18

Figure 5. Histogram of Six Month Creatinine Values for Azathioprine Treated Patients



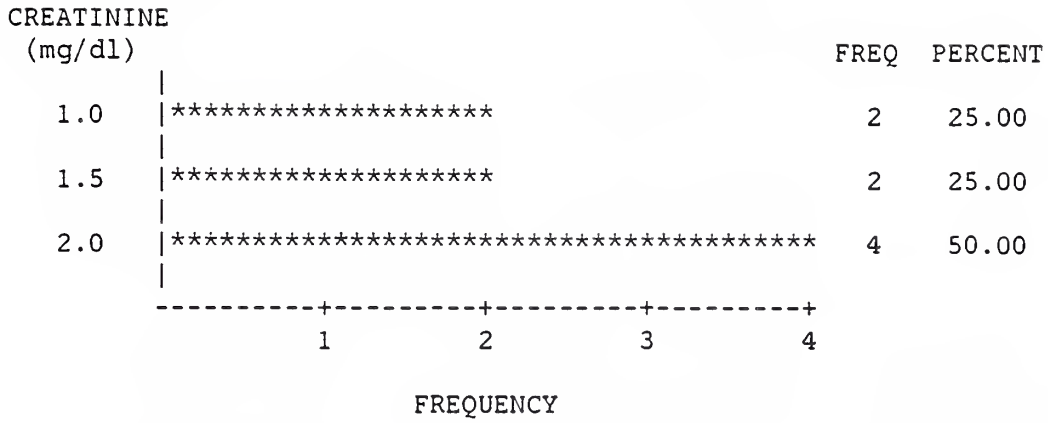
Mean=2.12
S.E.M.=.15

Figure 6. Histogram of Three Month Creatinine Values for Cyclosporine Treated Patients



Mean=2.16
S.E.M.=.20

Figure 7. Histogram of Six Month Creatinine Values
for Cyclosporine Treated Patients



Mean=1.66
S.E.M.=.21

Figure 8. Histogram of Three Month Creatinine Values for Azathioprine Failure Patients

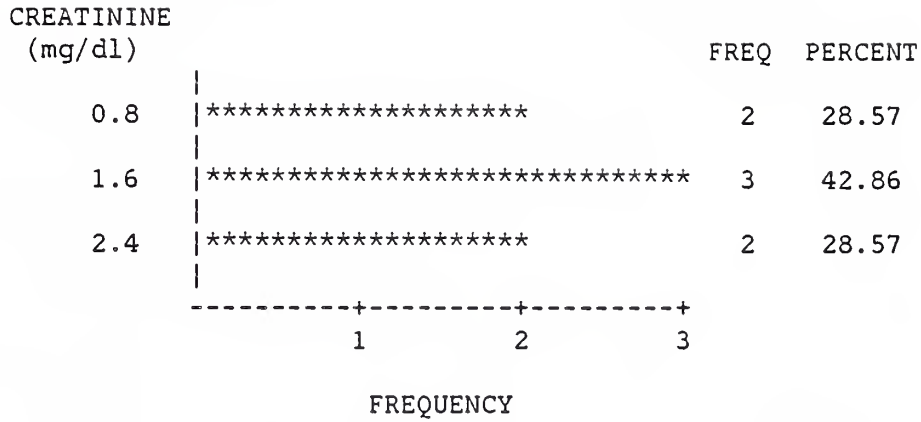


Figure 9. Histogram of Six Month Creatinine Values
for Azathioprine Failure Patients

Bibliography

1. Schwartz, R.S. and Damashed, W. "Drug-Induced Immunological Tolerance." Nature 183:1682-1683, 1959.
2. Calne, R.Y. "The Rejection of Renal Homografts - Inhibition in Dogs by 6-Mercaptopurine." Lancet I:417-418, 1960.
3. Zukoski, C.F., Lee, H.H. and Hume, D.M. "The Prolongation of Functional Survival of Canine Renal Homografts by 6-Mercaptopurine." Surg. Forum 11:470-472, 1960.
4. Elion, G.B., Callahan, S., Bieber, S., Hitchings, G.H. and Rundles, R.W. "A Summary of Investigations with 6-[(1-Methyl-4-Nitro-5-Imidazolyl)Thio]Purine (B.W. 57-322)." Cancer Chemotherapy Reports 14:93-98, 1961.
5. Calne, R.Y., Alexandre, G.P.J. and Murray, J.E. "A Study of the Effects of Drugs in Prolonging Survival in Homologous Renal Transplants in Dogs." Ann. N.Y. Acad. Sci. 99:743-761, 1962.
6. Murray, J.E., Merrill, J.P., Damin, G.J., Dealy, J.B., Alexandre, G.P.J. and Harrison, J.H. "Kidney Transplantation in Modified Recipients." Annals of Surgery 156:337-355, 1962.
7. Murray, J.E., Merrill, J.P., Harrison, J.H., Wilson, R.E. and Damin, G.I. "Prolonged Survival of Human Kidney Homografts by Immunosuppressive Drug Therapy." New England Journal of Medicine 268:1315-1323, 1963.
8. Kreis, H., Lacombe, M., Noel, L.H., Descamps, J.M., Chailley, J. and Crosnier, J. "Kidney Graft Rejection: Has There the Need for Steroids to be Re-evaluated?" Lancet II:1169-1172, 1978.
9. Starzl, T.E., Marchioro, T.L. and Wadell, W.R. "The Reversal of Rejection in Human Renal Homografts with Subsequent Development of Homograft Tolerance." Surgery Gynecology and Obstetrics 117:385-395, 1963.
10. Goodwin, W.E., Mims, M.M. and Kaufman, J.J. "Human Renal Transplantation III: Technical Problems Encountered in Six Cases of Kidney Homotransplantation." Trans. Am. Ass. Genitourin Surg. 54:116-123, 1962.
11. Borel, J.F. "A Comparative Study of In Vitro and In Vivo Drug Effects on Cell Mediated Cytotoxicity." Immunology 31:631-641, 1976.

12. Borel, J.F. "Effect of the New Anti-Lymphocyte Peptide Cyclosporin A in Animals." Immunology 32:1017-1025, 1977.
13. Calne, R.Y., White, D.J.G., Thiru, S., Evans, D.B., McMaster, R., Dunn, D.C., Craddock, G.N., Pentlow, B.D. and Rolles, K. "Cyclosporin A in Patients Receiving Renal Allografts from Cadaver Donors." Lancet II:1323-1327, 1978.
14. Calne, R.Y., Rolles, K., White, D.J.G., Thiru, S. Evans, D.B., McMaster, P., Dunn, D.C., Craddock, G.N., Henderson, R.G., Aziz, S. and Lewis, P. "Cyclosporin A Initially as the Only Immunosuppressant in 34 Recipients of Cadaveric Organs: 32 Kidneys, 2 Pancreases, and 2 Livers." Lancet II:1033-1036, 1979.
15. Bach, J.F. The Mode of Action of Immunosuppressive Agents. New York: American Elsevier, 1975.
16. Bach, M.A. and Bach, J.F. Activities of Immunosuppressive Agents in Vitro II. Different Timing of Azathioprine and Methotrexate in Inhibition and Stimulation of Mixed Lymphocyte Reaction." Clinical and Experimental Immunology 11:89-98, 1972.
17. Dimitriu, A. and Fauci A.S. "Differential Sensitivity of Human Lymphocyte Subpopulations to Azathioprine." Transplant. Proc. 11:878-881, 1979.
18. Duclos, H., Maillot, M.C., Kreis, H. and Galanaud, P. "T-Suppressor Cell Function Impairment in Peripheral Blood Lymphocytes from Transplant Recipients Under Azathioprine and Corticosteroids." Transplantation 28:437-438, 1979.
19. Bach, J.F. and Dardenne, M. "Antigen Recognition by T-Lymphocytes II. Similar Effects of Azathioprine, Antilymphocyte Serum and Antitheta Serum on Rosette-Forming Lymphocytes in Normal and Neonatally Thymectomized Mice." Cellular Immunology 3:11-21, 1977.
20. Alexandre, G.P., Murray, J.E., Dammin, G.J. and Nolan, B. "Immunosuppressive Drug Therapy in Canine Renal and Skin Homografts." Transplantation 1:432-461, 1963.
21. Zukoski, C.F., Callaway, J.M. and Rhea, W.G. "Prolongation of Renal Homograft Survival by Antimetabolites." Transplantation 1:293-297, 1963.
22. Krakauer, H., Grauman, J.S., McMullan, M.R. and Creede, C.C. "The Recent U.S. Experience in the Treatment of End-Stage Renal Disease by Dialysis and Transplantation." New England Journal of Medicine 308:1558-1563, 1983.

23. Morris, P. Kidney Transplantation - Principles and Practice (2nd ed.). London: Grune and Stratton, 1984.
24. Haxhe, J.J., Alexandre, G.P.J. and Kestene, P.J. "The Effect of Immuran and Azaserine on Liver Function Tests in the Dog." Arch. Int. Pharmacodyn. Ther. 168:366-372, 1967.
25. Penn, I. "Tumor Incidence in Human Allograft Recipients." Transplant. Proc. 11:1047-1057, 1979.
26. d'Apice, A.J.F. "Non-Specific Immunosuppression: Azathioprine and Steroids." in Kidney Transplantation - Principles and Practice (editor P.J. Morris) (2nd edition). London: Grune and Stratton, 1984.
27. Cupps, T.R. and Fauci, A.S. "HLA-DR Antigens: Structure, Separation of Subpopulations, Gene Cloning and Function." Immunological Reviews 65:132-155, 1982.
28. Dupont, E., Berkenboom, G., Leempoel, M. and Potliege, P. "Failure of Dexamethasone to Induce In Vitro Lysis of Human Mononuclear Cells." Transplantation 30:387-389, 1980.
29. Gillis, S., Crabtree, G.R. and Smith, K.A. "Glucocorticoid-Induced Inhibition of T Cell Growth Factor Production II. The Effect on the In Vitro Generation of Cytolytic T Cells." Journal of Immunology 123:1632-1638, 1979.
30. Snyder, D.S. and Unanue, E.R. "Corticosteroids Inhibit Murine Macrophage Ia Expression and Interleukin-1 Production." Journal of Immunology 129:1803-1805, 1982.
31. Goodwin, W.E., Kaufman, J.J., Mims, M.M., Turner, R.D., Glasscock, R., Goldman, R. and Maxwell, M.H. "Human Renal Transplantation I. Clinical Experience with Six Cases of Renal Homotransplantation." Journal of Urology 89:13-24, 1963.
32. Hamburger, J., Vaysse, J., Crosnier, J., Auvert, J., Lalanne, C.M. and Hopper, J., Jr. "Renal Homotransplantation in Man after Radiation of the Recipient." American Journal of Medicine 32:854-871, 1962.
33. Bach, J.F. and Leski, M. "The Rejection Crisis in Human Renal Transplantation." Eur. J. Clin. Biol. Res. 15:1048-1053, 1970.
34. Strom, T.S. "Immunosuppressive Agents in Renal Transplantation." Kidney International 26:353-365, 1984.

35. Powles, R.L., Clink, H.M., Spence, D., Morgenstern, G., Watson, T.G., Selby, P.J., Woods, M., Barrett, A., Jameson, B., Sloane, J., Lawler, S.D., Kay, H.E.M., Lawson, D., McElwain, T.J. and Alexander, P. "Cyclosporin A to Prevent Graft-Versus-Host Disease in Man after Allogeneic Bone-Marrow Transplantation." Lancet I:327-329, 1980.
36. Calne, R.Y. "Immunosuppression for Organ Grafting. Observations on Cyclosporin A." Immunological Reviews 46:113-124, 1979.
37. Calne, R.Y. "Cyclosporin A in Renal Transplantation." In Advances in Nephrology, Vol. 10. (Edited by Hamburger, J., Crosnier, J., Grunfeld, J.P. and Maxwell, M.H.) Chicago: Year Book Medical Publishers, 1980.
38. Morris, P.J. "Cyclosporin A." Transplantation 32:349-354, 1981.
39. Carta, N.P., Cullen, P.R., Thompson, J.F., Bewick, A.L., Wood, R.F. and Morris, P.J. "Monitoring Lymphocyte Populations in Renal Allograft Recipients." Transplant. Proc. 15:1157-1159, 1983.
40. Kahan, B.D., Kerman, R.H., Agostino, G., Friedman, A. and Legrue, S.J. In Cyclosporin A, pp.281-293, (Edited by White, D.J.) Amsterdam: Elsevier Biomedical, 1982.
41. Bunjes, D., Hardt, C., Sollack, W., Deusch, K., Rollingshoff, M. and Wagner, H. In Cyclosporin A, pp.261-280, (Edited by White, D.J.) Amsterdam: Elsevier Biomedical, 1982.
42. Larsson, E.L. "Cyclosporin A and Dexamethasone Suppress T Cell Responses by Selectively Acting at Distinct Sites of the Triggering Process." Journal of Immunology 124: 2828-2833, 1980.
43. Palacios, R. and Moller, G. "Cyclosporin A Blocks Receptors for HLA-DR Antigens on T-Cells." Nature 290: 792-794, 1981.
44. Nemlander, A., Ahonen, J., Wiktorowicz, K., Von Willebrand, E., Hekali, R., Lalla, M. and Hayry, P. "Effect of Cyclosporine on Wound Healing." Transplantation 36:1-6, 1983.
45. Keown, P.A., Stiller, C.R., Ulan, R.A., Sinclair, N.R., Wall, W.J., Caruthers, G. and Howson, W. "Immunological and Pharmacological Monitoring in the Clinical Use of Cyclosporin A." Lancet I:686-689, 1981.

46. Morris, P.J., French, M.E., Tiong, A., Frostick, J. and Hunnisset, A. In Cyclosporin A, pp.355-364, (Edited by White, D.J.) Amsterdam: Elsevier Biomedical, 1982.
47. Calne, R.Y., White, D.J.G., Rolles, K., Smith, D.P. and Herbertson, B.M. "Prolonged Survival of Pig Orthotopic Heart Grafts Treated with Cyclosporin A." Lancet I: 1183-1186, 1978.
48. Dunn, D.C., White, D.J.G., Herbertson, B.M. and Wade, J. "Prolongation of Kidney Survival During and After Cyclosporin A Treatment." Transplantation 27:359-361, 1979.
49. Green, L.J. and Allison, A.C. "Extensive Prolongation of Rabbit Kidney Allograft Survival After Short-Term Cyclosporin A Treatment." Lancet I:1182-1185, 1978.
50. Homan, W.P., Falne, J.W. and Morris, P.J. "Nature of the Unresponsiveness Induced by Cyclosporin A in Rats Bearing Renal Allografts." Transplantation 28:439-441, 1979.
51. Jamieson, S.W., Burton, N.A., Bieber, C.P., Reitz, B.A., Dyer, P.E., Stimson, F.B. and Shumway, N.E. "Cardiac-Allograft Survival in Primates Treated with Cyclosporin A." Lancet I:545, 1979.
52. Homan, W.P., Fabre, J.W., Millard, P.R. and Morris, P.J. "Interaction of Cyclosporin A with Antilymphocyte Serum and with Enhancing Serum for the Suppression of Renal Allograft Rejection in the Rat." Transplantation 29:219-222, 1980.
53. Fletcher, S.M., Kerman, R.H., van Buceu, C., Payne, W.S. and Kahan, B.D. "The Use of Cyclosporin and Prednisone for High MLC Haploidentical Living Related Renal Transplants." Transplant. Proc. 15:442-445, 1983.
54. French, M.E., Thompson, J.F., Hunnisset, A.G., Wood, R.F. and Morris, P.J. "Impaired Function of Renal Allografts During Treatment with Cyclosporin-A: Nephrotoxicity or Rejection?" Transplant. Proc. 15:485-488, 1983.
55. Hedley, D., Powles, R.L. and Morgenstern, D. In Cyclosporin A, pp.209-231, (Edited by White, D.J.) Amsterdam: Elsevier Biomedical, 1982.
56. Calne, R.Y. and White, D.J. "The Use of Cyclosporin A in Clinical Organ Grafting." Annals of Surgery 196: 330-337, 1982.

57. Homan, W.P., French, M.E. and Morris, P.J. "Effect of Cyclosporin A upon the Function of Ischemically Damaged Renal Autografts in the Dog." Transplantation 30:228-230, 1980.
58. Whiting, P.H., Thomson, A.W., Blair, J.T. and Simpson, J.G. "Experimental Cyclosporin A Nephrotoxicity." British Journal of Experimental Pathology 63:88-94, 1982.
59. Hedley, D., Powles, R.L. and Morgenstern, G.R. In Cyclosporin A, pp.545-551, (Edited by White, D.J.) Amsterdam: Elsevier Biomedical, 1982.
60. Klintman, G.B., Iwatsuki, S. and Starzl, T.E. "Cyclosporin A Hepatotoxicity in 66 Renal Allograft Recipients." Transplantation 32:488-489, 1981.
61. Klintman, G.B., Iwatsuki, S. and Starzl, T.E. "Nephrotoxicity of Cyclosporin in Liver and Kidney Transplant Patients." Lancet I:470-471, 1981.
62. Lakiec, F., Poirier, O. Gluckman, E. and Devergie, A. In Cyclosporin A, pp.497-500, (Edited by White, D.J.) Amsterdam: Elsevier Biomedical, 1982.
63. Powell-Jackson, P.R., Young, B., Calne, R.Y. and Williams, R. "Nephrotoxicity of Parenterally Administered Cyclosporine After Orthotopic Liver Transplantation." Transplantation 36:505-508, 1983.
64. Tutschka, P.J., Hess, A.D., Beschorner, W.E. and Santos, G.W. In Cyclosporin A, pp.519-538, (Edited by White, D.J.) Amsterdam: Elsevier Biomedical, 1982.
65. French, M.E., Thompson, J.F., Hunnisset, A.G., Wood, R.F. and Morris, P.J. "Impaired Function of Renal Allografts During Treatment with Cyclosporin-A: Nephrotoxicity or Rejection?" Transplant. Proc. 15:485-488, 1983.
66. Cohen, D.J., Loertscher, R., Rubin, M.F., Tilney, N.L., Carpenter, C.B. and Strom, T.B. "Cyclosporine: A New Immunosuppressive Agent for Organ Transplantation." Annals of Internal Medicine 101:667-682, 1984.
67. Najarian, J.S., Ferguson, R.M., Sutherland, D.E.R., Rynasiewicz, J.J. and Simmons, R.L. "A Prospective Trial of the Efficacy of Cyclosporine in Renal Transplantation at the University of Minnesota." Transplant. Proc. 15:438-441, 1983.
68. Ost, L., Groth, C.G., Lindholm, B., Lundgren, G., Magnusson, G. and Tillegard, A. "Cadaveric Renal Transplantation in Patients of 60 Years and Above." Transplantation 30:339-340, 1980.

69. Thiru, S., Calne, R.Y. and Nagington, J. "Lymphoma in Renal Allograft Patients Treated with Cyclosporin-A as One of the Immunosuppressive Agents." Transplant. Proc. 13: 359-364, 1981.
70. Bird, A.G., McGlachlan, S.M. and Britton, J. "Cyclosporin A Promotes Spontaneous Outgrowth In Vitro of Epstein-Barr Virus-Induced B-Cell Lines." Nature 289:300-301, 1981.
71. Starzl, T.E., Weil, R., Iwatsuki, S., Klintmalm, G.I., Schroter, G.P., Koep, L.J., Iwaki, Y., Terasaki, P.I. and Porter, K.A. "The Use of Cyclosporin A and Prednisone in Cadaver Kidney Transplantation." Surgery Obstetrics and Gynecology 151:17-26, 1980.
72. Calne, R.Y., White, D.J.G., Evans, D.B., Thiru, S., Henderson, R.G., Hamilton, D.V., Rolles, K., McMaster, P., Duffy, T.G., MacDougall, B.R.D. and Williams, R. "Cyclosporin A in Cadaveric Organ Transplantation." British Medical Journal 382:934-936, 1981.
73. Merion, R.M., White, D.J.G., Thiru, S., Evans, D.B. and Calne, R.Y. "Cyclosporine: Five Years Experience in Cadaveric Renal Transplantation." New England Journal of Medicine 309: 148-154, 1984.
74. Canadian Multicenter Transplant Study Group. "A Randomized Clinical Trial of Cyclosporine in Cadaveric Renal Transplantation." New England Journal of Medicine 309: 809-815, 1983.
75. European Multicenter Trial Group. "Cyclosporin in Cadaveric Renal Transplantation: One-Year Follow-Up of a Multicentre Trial." Lancet II:986-989, 1983.
76. Homan, W.P., French, M.E., Millard, P.R. and Morris, P.J. "A Study of Eleven Drug Regimens Using Cyclosporin-A to Suppress Renal Allograft Rejection in the Dog." Transplant. Proc. 13:397-401, 1981.

TABLE A1. SUMMARY OF DATA COLLECTED ON RENAL TRANSPLANT RECIPIENTS

	T	S	D			L	L	D	D	C			P	S	O	I								
			A	A	M					O	O	R					R	R						
O	X	O	B	B	A	O	S	Y	Y	E	E	E	A	A	R	W								
B	D	U	E	P	B	R	S	S	S	J	J	J	T	T	E	I								
S	A	R	A	E	R	T	6	1	6	1	6	1	S	3	6	C								
	T	P	C	G	I	F	A	E	A	M	Y	M	Y	E	M	M	Y							
	E	T	E	E	C	T	K	C	L	O	R	O	R	R	O	O	C							
1	021983	A	M.K.	C	38	N	1	0	0	A	N	N	35	50	1	2	2	2.4	2.3
2	040183	A	S.G.	C	27	N	2	95	60	A	N	N	61	88	1	2	2	2.1	1.8
3	040883	A	D.S.	C	48	N	1	3	0	A	Y	Y	152	163	2	2	2
4	040983	A	T.M	C	35	N	1	3	0	A	Y	Y	27	27	1	1	1
5	041483	A	T.G.	C	34	N	1	48	33	D	Y	Y	45	45	1	1	1
6	042883	A	K.G.	L	32	N	1	.	.	A	N	N	14	14	0	0	0	1.2	1.2
7	052283	A	K.W.	C	32	N	1	0	0	A	Y	Y	55	55	1	1	1
8	053183	A	B.C.	L	27	N	1	0	0	A	N	N	39	39	1	1	0	2.4	2.3
9	060783	A	H.B.	C	23	N	1	5	0	A	N	N	18	18	0	0	0	1.7	1.4
10	061783	A	S.S.	C	22	N	1	0	0	A	N	N	29	29	1	1	1	2.1	1.7
11	062583	A	A.L.	C	26	Y	1	3	0	A	N	N	20	20	0	0	0	1.0	1.0
12	070683	A	R.T.	C	22	N	2	50	30	A	N	N	55	55	3	3	1	3.4	4.2
13	070783	A	G.R.	L	20	N	1	0	0	A	N	N	19	19	1	1	0	1.2	1.0
14	071283	A	N.B.	L	37	N	1	.	.	A	N	N	17	17	1	1	0	1.0	1.0
15	071483	A	S.F.	L	19	N	1	0	0	A	N	N	48	48	2	2	1	1.5	1.6
16	072683	A	C.B.	L	16	N	1	.	.	A	N	N	21	21	1	1	0	1.6	1.5
17	072883	A	J.M.	C	41	N	1	3	3	A	Y	Y	20	20	1	1	1
18	080483	A	J.V.	L	57	N	1	0	0	A	N	N	14	30	0	0	0	2.0	2.1
19	080483	A	R.B.	L	15	N	1	.	.	A	N	N	59	59	0	0	0	1.1	1.0
20	081383	A	W.K.	C	11	N	1	30	10	A	Y	Y	8	8	1	1	1
21	081783	A	F.S.	C	45	N	1	20	0	A	N	N	40	40	1	1	1	1.5	1.3
22	082083	A	J.B.	C	18	N	2	5	3	A	N	N	47	47	1	1	1	1.1	0.9
23	090283	A	R.M.	C	41	N	3	10	10	A	N	N	61	71	1	1	1	2.0	2.0
24	091083	A	A.J.	C	42	N	1	3	0	A	N	N	38	38	1	1	1	.	1.6
25	091483	A	D.A.	C	40	N	1	0	0	A	N	N	61	61	2	2	1	.	1.9
26	091883	A	D.L.	C	40	N	1	0	0	A	Y	Y	51	51	1	1	1
27	092283	A	D.M.	L	40	N	1	.	.	A	N	N	17	53	1	2	1	1.1	1.2
28	092883	A	W.K.	C	11	N	2	58	58	A	N	N	35	35	1	1	1	0.6	2.0
29	110683	A	A.S.	C	50	N	1	0	0	A	Y	Y	61	61	1	1	1
30	111083	A	M.H.	L	6	N	1	.	.	A	N	N	12	12	0	0	0	0.4	0.5
31	112983	A	G.L.	C	54	N	1	0	0	A	Y	Y	53	53	1	1	1
32	121383	A	J.M.	L	47	N	1	.	.	A	N	N	28	28	1	1	0	1.2	1.1
33	012684	A	W.G.	L	29	N	1	.	.	A	N	N	40	40	1	1	1	1.3
34	020984	A	M.A.	L	16	N	1	.	.	A	N	N	13	13	0	0	0	1.0	1.2
35	032184	A	D.O.	C	44	N	1	5	0	D	Y	Y	60	60	1	1	1
36	032384	A	M.L.	L	50	Y	1	0	0	A	N	N	25	25	1	1	0	1.3
37	032984	A	R.B.	L	48	Y	1	0	0	D	N	Y	95	165	4	4	3	2.1	6.3
38	040984	A	T.S.	C	33	N	1	3	0	A	N	N	64	64	2	2	1	2.2	1.9
39	041084	A	Y.S.	L	33	Y	1	3	0	D	Y	Y	1	1	0	0	0

TABLE A1. SUMMARY OF DATA COLLECTED ON RENAL TRANSPLANT RECIPIENTS
(continued)

	T	S	D				C				P		T										
			A	A	M	O	A	A	R	R	R	E	E	S	O	I							
	X	O	B	G	B	A	O	S	S	Y	Y	E	E	E	A	A	R	W	S	M			
	D	U	E	R	P	B	R	S	S	S	J	J	J	T	T	E	I	T	E	T			
O	A	R	A	T	A	E	R	T	6	1	6	1	6	1	S	3	6	C	T	R			
B	T	P	C	G	I	F	A	E	A	M	Y	M	Y	E	M	M	Y	C	E	E			
S	E	P	E	E	C	T	K	C	L	O	R	O	R	O	R	O	O	C	H	J	J		
40	051784	A	D.B.	L	38	N	1	3	3	A	N	N	20	41	1	2	0	1.7	1.9
41	052284	A	W.B.	C	42	N	1	5	5	A	N	N	35	35	1	1	1	1.0	1.0
42	053084	A	A.T.	C	15	N	1	3	0	A	N	N	37	37	2	2	0	1.2	1.2
43	062184	A	L.R.	L	11	N	1	.	.	A	N	N	23	23	0	0	0	0.9	0.8
44	073184	A	J.L.	L	17	N	1	.	.	A	N	N	64	64	1	1	1	1.6	1.9
45	081184	A	J.A.	C	41	N	1	3	3	A	N	N	83	114	1	2	2	1.7	1.4
46	091184	A	L.L.	C	38	N	1	0	0	A	N	N	32	32	1	1	1
47	100984	A	A.B.	C	43	N	1	0	0	A	Y	Y	11	11	1	1	1
48	103084	A	D.O.	L	22	N	1	0	0	A	N	N	18	18	0	0	0	1.1	1.2
49	112784	A	K.P.	L	13	N	1	0	0	A	N	N	39	39	2	2	1	1.3	1.3
50	120383	C	M.W.	C	54	N	1	13	5	D	N	Y	101	116	1	1	0	3.9	2.1	1	.	.	.
51	120483	C	B.G.	C	50	N	1	0	0	A	N	Y	53	57	1	1	0	2.1	3.2	0	.	.	.
52	121383	C	L.I.	C	62	N	1	33	8	A	N	N	101	148	1	1	0	1.6	2.2	0	7	0	.
53	122483	C	C.H.	C	52	N	3	3	3	A	N	N	23	23	0	0	0	2.8	2.7	0	6	0	.
54	122483	C	H.V.	C	28	N	3	60	33	A	Y	Y	18	18	1	1	1	.	.	0	.	.	.
55	012984	C	K.J.	C	34	Y	1	13	0	D	Y	Y	72	72	1	1	0	2.4	.	1	.	.	.
56	021184	C	M.B.	C	23	N	3	95	93	D	Y	Y	167	351	2	2	1	.	.	0	.	.	.
57	021684	C	W.R.	C	49	Y	1	3	3	A	N	N	45	45	1	1	0	1.8	2.2	0	9	0	.
58	022284	C	R.B.	C	51	Y	1	30	30	A	N	N	19	45	0	1	0	1.6	1.5	0	7	1	8
59	030784	C	D.P.	C	35	Y	1	10	10	A	N	N	16	32	0	0	0	1.5	1.3	0	7	0	.
60	031384	C	E.P.	C	49	N	1	18	5	A	N	N	36	36	1	1	0	1.7	1.5	0	6	0	.
61	031584	C	S.H.	C	55	N	1	0	0	A	N	N	65	65	2	2	1	2.3	3.5	0	10	0	.
62	032884	C	R.V.	C	51	Y	1	0	0	D	Y	Y	3	3	0	0	0	.	.	1	.	.	.
63	033084	C	D.B.	C	24	N	2	23	23	A	N	N	38	38	1	1	0	2.5	.	0	3	0	.
64	042684	C	C.M.	C	45	N	2	0	0	A	N	N	38	38	1	1	1	2.1	2.9	0	7	0	.
65	062084	C	J.D.	C	39	N	1	3	0	A	N	N	72	72	2	2	1	2.0	1.6	27	.	.	.
66	072484	C	M.M.	C	50	N	1	33	3	D	Y	Y	57	57	1	1	1	.	.	1	.	.	.
67	072984	C	I.P.	C	51	N	1	3	0	A	N	N	45	54	1	1	1	3.9	4.5	0	6	1	2
68	091284	C	F.S.	C	56	N	1	15	5	A	N	N	28	52	1	3	1	2.4	2.5	19	7	1	4
69	110484	C	J.A.	C	32	N	1	95	3	A	N	N	64	105	1	2	1	1.8	1.7	3	4	0	.
70	121484	C	L.M.	C	31	Y	1	60	0	A	N	N	72	72	2	2	1	2.3	.	0	.	.	.
71	122884	C	L.A.	C	12	N	2	5	0	A	N	N	26	26	0	0	0	1.2	1.2	7	.	.	.
72	013085	C	F.M.	C	60	N	1	5	0	A	N	N	17	29	0	0	0	1.2	1.2	0	4	0	.
73	020185	C	R.K.	C	51	N	2	5	3	A	N	N	25	37	0	1	0	1.6	1.6	4	6	1	1
74	020885	C	H.M.	C	57	N	1	8	0	A	N	N	36	36	1	0	0	2.1	1.8	17	4	0	.
75	021785	C	P.T.	C	42	N	2	13	13	A	N	N	38	38	2	2	1	1.8	1.8	19	6	0	.
76	081883	F	L.D.	C	40	N	1	77	77	A	N	N	47	93	1	2	2	1.7	1.5	197	.	.	.
77	112383	F	A.W.	C	56	N	1	8	0	A	N	N	79	79	2	2	2	1.7	1.7	30	.	.	.
78	012084	F	M.M.	C	8	N	1	0	0	A	N	N	44	44	1	1	1	0.6	0.7	27	.	.	.

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