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Renal Transplantation in End Stage Renal Disease

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Sixty patients with renal transplants were fellowed for 1 to 54 months. During this period 14 patients died. Overall patient survival was 77%. Out of 61 transplants, 43 are functional; overall graft survival being 71%. cumulative patient survival at 18 months was 69% and Cumulative functional graft survival was 65%. The results in recipients of allograft from live related donors were significatnly better than those from live unrelated donors. Pateint and graft suvival rates were 93% in live related transplants. Patient survival rate was 63% and graft survival rate was 54% in live unrelated transplants.

Rejection was the most common cause of loss of graft and sepsis was the most common cause of death of these patients. Rejection, scyclosporine induced nephrotoxicity, hepatic dysfunction, herpes zoster infections, hypertension were frequent complications occuring in 5 or more pateints. Cyclosporine dosage has to be regualted very carefully because of its toxic effect and interaction with other drugs. A comparasion of long term results of transplants between diabetics and non-diabtics and non-diabetics and in different age groups did not show any significant difference. There seems to be little doubt that allografts from living related sources are extremely successful as treatment for chronic renal failure with relatively high success rate and low morbidity, this treatment seems to be the treatment of choice for many patients.

Kidney transplantation and chronic dialysis have evolved into acceptable forms of therapy for end stage renal disease. Chronic dialysis is extremely useful but carries with it high morbibity and mortality and it is far less successful in the total rehabilitation of the person. Transplantation may be ideal therapy for many but most of the patients are denied because of lack of facilities in this country and also because of non-availability of the kidneys. Less than 20% of the patients get live related kidney transplants (1). Facilities for cadaver kidney transplantation are not available in Pakistan or in the neighbouring country. Cost of transplantation especially for cadaveric kidney in U.K. or U.S.A. is so high that most of our patients can not afford it. Recently, because of availability of kidneys from non related living donors and low cost, many of our patients have proceeded to India to have renal transplanation.

The purpose of this study was:

(a) to study long term survival rates of various types of renal transplants.
(b) to study the complications and the results of different immunosuppressive regimens in these patients.

PATIENTS AND METHODS

Sixty patients who had undergone renal transplantation between November, 1982 to May, 1987, formed the basis of this report. All these patients were diagnosed to have end stage renal disease on the basis of history, examination blood chemistry, ultrasonography and radioisotopic studies. Conservative management alone was not sufficient to keep these patients symptom free. Most of them underwent some form of dialysis while some were refferred abroad before they had any dialytic therapy in the country. These patients rturned between two weeks to four months after transplantation. Seven patients had transplantation done in Pakistan. They were on different regimens of immunosuppression and were properly followed up. Blood urea, creatinine, urine, haemoglobin, total leukocyte count and liver functions were checked regularly. Ultrasonography, renal scans and renograms were done whenever there was increase in blood urea and creatinine. Blood cyclosporine levels were done when available. Biopsies of transplanted kidneys were taken in some cases of decreasing renal function. Diagnosis of rejections or cyclosporine toxicity was made on clinical grounds and on the basis of above laboratory tests. In case of rejection 500 mg. of methyle prednisolone was given I/V daily for four days.

Other complications occuring in these patients were also noted and treated accordingly. Cummulative survival rates were calculated by actuarial method and student's test was used for evaluating the statistical significance.

RESULTS

The age and sex distribution of these 60 patients 49 males, 11 females, is shown in Table-1. It reveals that 19 patients were between 21 and 30 years 17 between 31 and 40 and 15 between 41 and 50 years. Only 4 patients were less than 20 years and 5 more than 50 years of age.

TABE 1

AGE GROUPS

AGRE GROUPS	MALE	FEMALE	TOTAL
Less and 20	1	3	4
21 – 30	16	3	19
31 – 40	14	3	17
41 – 50	14	1	15
51 – 60	4	1	5
Total:	49	11	60

Table-2. shows the original diagnosis in cases studied. Out of 60 cases, 18 patients had chronic glomerulorephritis, 17 hypertension, 7 diabetic nephropathy, 4 rapidly progressive glomerulnephritis, 2 polycystic disease, 2 calculus renal failure, 3 chronic pyelonephritis and in 5 patients cause of chronic renal failure could not be determined.

Table-3 shows the types of dialysis which these patients had before transplant. 15 patients had continuous ambulatory peritoneal dialysis for 2 to 13 months (means 6 ± 3.2 months). Out of them 5 patients underwent continuous ambulatory peritoneal dialysis for 6 months or more. 16 patients had chronic haemodialysis for 2 to 12 months (mean 4.1 ± 3.10 months), 3 patients were on haemodialysis for 6 months or more, while 13 patients had acute haemodialysis abroad. 12 patients had acute peritoneal dialysis once or twice here and then had acute haemodialsis for one to three months (mean 1.9 ± 0.8 months).

TABLE – 2

1.	Ch. glomerulonephritis	18
2.	Hypertension	17
3.	Diabetic nephropathy	7
4.	Chronic renal failure (unknown origin)	5
5.	Rapidly progressive Glomerulonephritis.	4
6.	Ch. Pyelonephritis	3
7.	Polycystic disease	2
8.	Calculus renal failure	2
9.	Focal segmental glomerulosclerosis.	2

TABLE – 3

PRE TRANSPLANTATION TREATMENT

Treatment	No. of patients	Durations of treatment (months)			No. of case with more than 6 months treatment
		Range	Mean	± S.D.	
C.A.P.D.	15	2-13	6	± 3.2	5
Ch. Haemo.	16	2-12	4.1	± 3.1	3
Ac. Haemo.	13	1-2	1.3	± .4	–
APD+HAEMO.	12	1-4	1.9	± .8	–
CAPD+HAEMO.	5	2-9	6.4	± 2.9	3

Five patients were started on continous ambulatory peritoneal dialysis but after 2 to 5 months were changed to haemodialysis because of complications related to continuous ambulatory peritoneal dialysis. Three patients had this combined therapy for more than 6 months. Mean duration of this type of therapy was 6.4 ± 2.9 months.

Table-4 shows the transplant centers and types of transplants in 60 patients (61 transplants). In one patient transplant was done twice. Two patients had transplant in U.S.A. Both transplants were from cadaver source. In seven patients transplant was done in Pakistan, 6 were live-related donors and one was live unrelated donor. One had live related donor transplant done in Norway. 11 patients

TABLE – 4

TRANSPLANT CENTRES

COUNTRY	LIVE RELATED	LIVE UN RELATED	CADAVER
U.S.A.	–	–	2
PAKISTAN	6	1	–
ENGLAND	7	4	1
INDIA	–	39	–
NORWAY	1	–	–
	14	44	3

had transplant done in England, 7 were live related, 4 live unrelated and one was cadaver. 38 patients underwent renal transplantation 39 times in India, all from live unrelated donors.

As regards HLA matching, one patient had a well matched graft while 53 patients had 50% matching. Direct lymphocyte cross match was negative in all cases. Records of HLA matching were not available for seven cases.

Three different regimens were used for immunosuppression. Nine patients received azathioprine and prednisolone, 14 patients got prednisolone and cyclosporine. In 38 patients prednisolone, cyclosporine and azathioprine were used. Maintenance dose of prednisolone given was 0.17 to 0.20 per kg. and of cyclosporine 3 to 6 mg/kg. Azathioprine was given in doses of 2 mg. per kg, when used in combination with prednisolone and as 50 mg. daily when tripple therapy was used.

Fig-1 shows the duration of follow up and the results in 60 patients out of whom 14 patients died. The overall mortality was 23% and overall patient survival rate was 77%.

Fig-2 shows results of functional graft survival. Overall functional survival rate was 71%; 43 of 61 grafts still functioning

Fig- 3 shows cumulative patient survival rates in live related live unrelated and cadaver renal transplants. Cumulative patient survival rate was 93% in recipients of live related, 67% in cadaver, 63% in live unrelated allografts

Fig. 1. Pateint Survival in Months

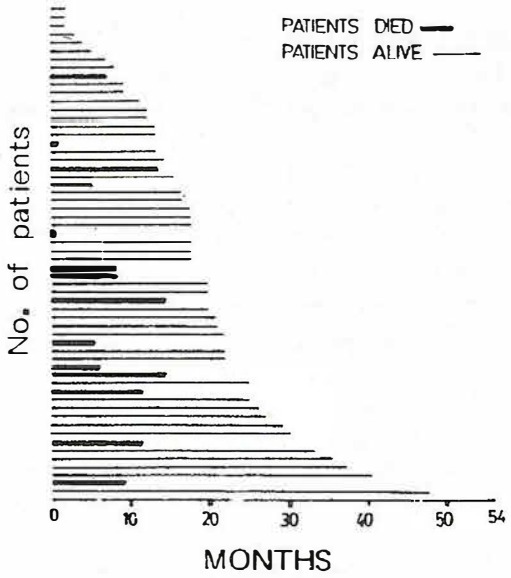
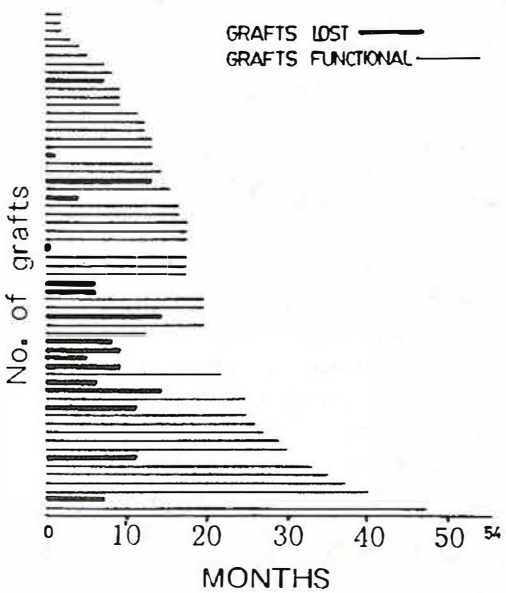


Fig. 2. Functional Grafts Survival in Months



with an overall survival rate of 69%. Difference in results of live related and live unrelated transplants was statistically significant (P. value < 0.05)

Fig-4 shows cumulative functional graft survival rates at 18 months. These were 93% in live related 67% in cadaver, 54% in live unrelated and 65% in all transplants. Difference between results of live related and live unrelated was statistically significant (P. value< 0.05).

Fig. 3. Cumulative Patient Survival.

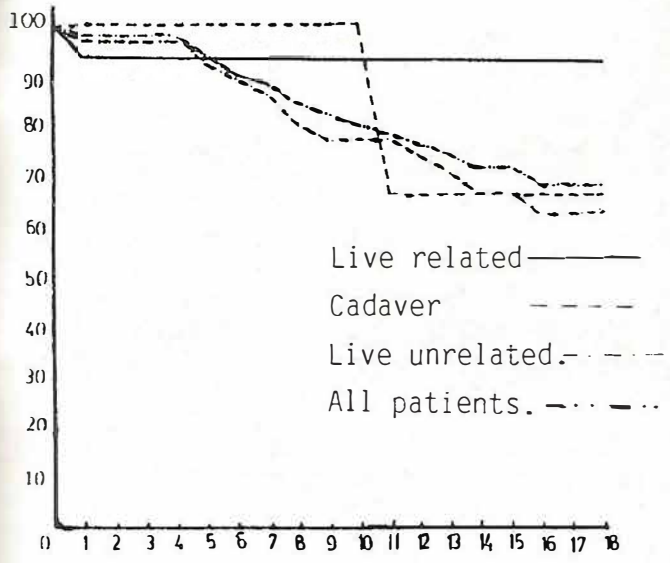


Fig. 5. Cumulative Patient Survival in Diabetic and Non Diabetic Patients

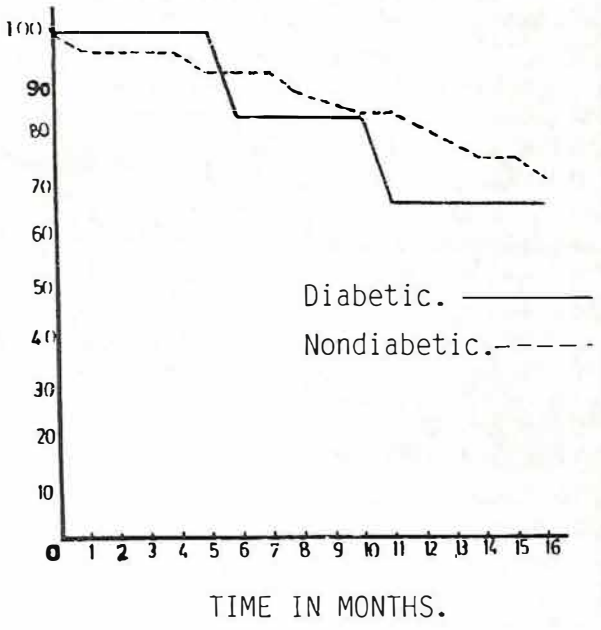


Fig. 4. Cumulative Functional Graft Survival

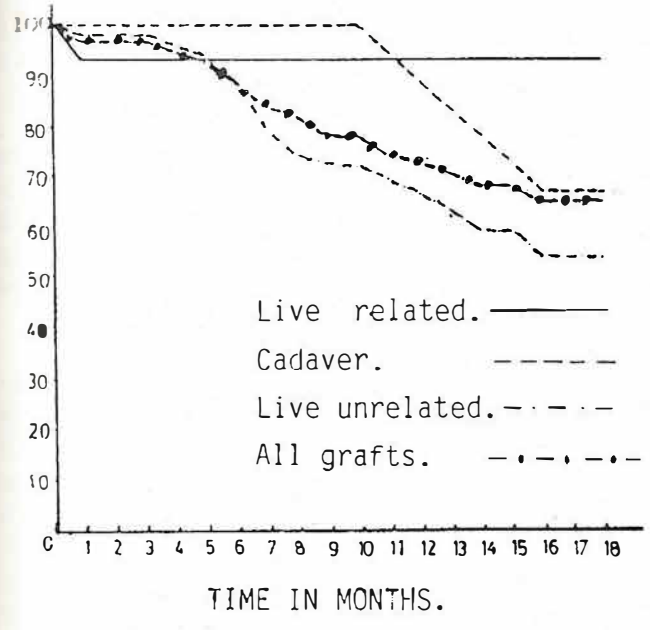


Fig. 6. Cumulative Functional Graft Survival in 3 Immuno Suppressive Treatment Groups.

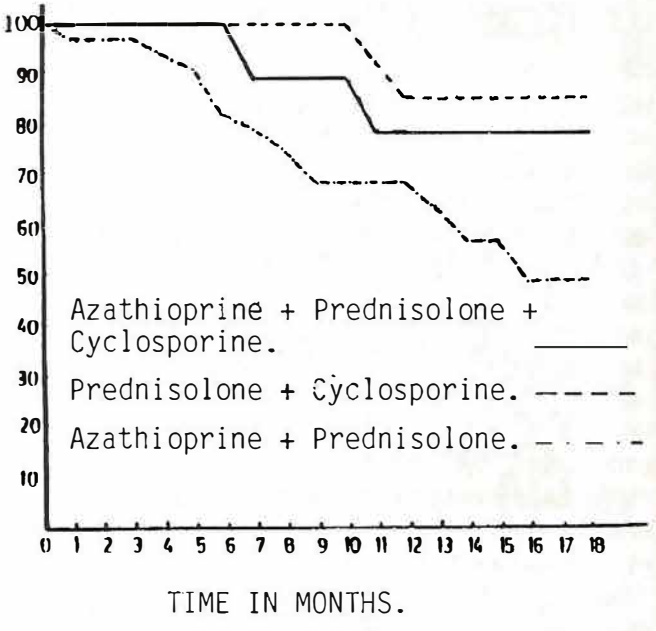


Fig-5 shows cumulative patient survival in diabetics (66%) and in non-diabetics (71%). The difference was statistically not significant.

Fig-6. shows cumulative patient survival rates in three different immunosuppression treatment groups. In azathioprine/prednisolone group cumulative survival at 18 months was 70%, in prednisolone/cyclosporine group 85% and in prednisolone/cyclosprine/azathioprine group it was 49%. The differences between prednisolone cyclosprine group and tripple therapy group was statistically significant (P. value$<$0.05)

Fig. 7. Cumulative Graft Survival in Different Age Groups.

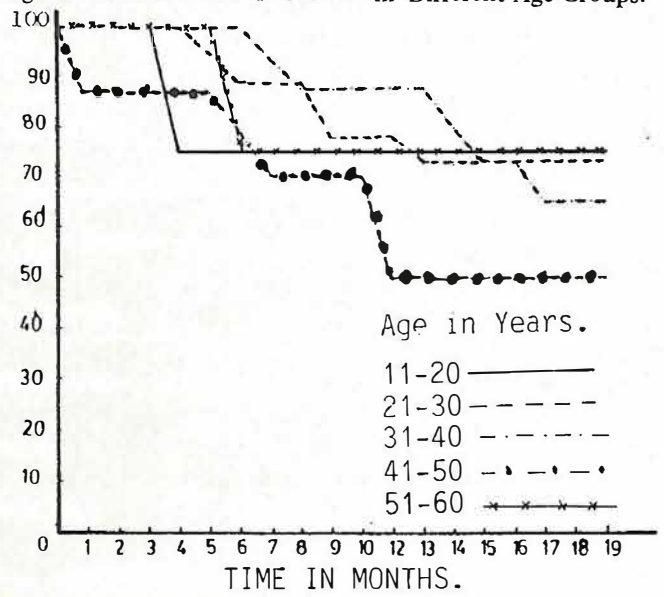


Fig-7 shows outcome of renal transplants in different age groups. The cumulative survival rate for patients in the age group of 10 to 20 years and 50 to 60 years was 75%. The cumulative survival rates for the patient in third decade were 73%, in 4th decade 63% and for patients in 5th decade 50% at 18 months. The differences among different age groups were not statistically significant.

Table-5 shows complications occuring in these patients Most common was renal dysfunction due to cyclosporine nephrotoxicity. This was seen in 20 patients and responded to decrease in dose of cyclosporine. Minor rejection episodes were seen in 14 patients which responded to Inj. Methl Prednisolone. Rejection episodes resulting in loss of graft occured in 10 cases, hypertension in 12, herpes zoster in 6, tuberculosis in 5, urinary tract infection in 5, septicemia in 5, acid peptic disease in 4, tinea versicolor infections in 4, pneumonia in 4, hepatitis in 3, hirsutism in 3, tremors in 3, mild hepatic dysfunction responding to decrease in cyclosporine in 3, peripheral vascular insufficiency in 2, recurrence of original disease in 1, renal artery stenosis in 1, diabetes mellitis in 1 and ureteric obstruction in 1. Out of these complications herpes zoster, hirsutism, tremors, nephrotoxicity, peripheral vascualr disease, liver dysfunction were seen only in patients treated with cyclosporine.

Table-6 shows the causes of death in these patients. Graft rejection with sepsis resulted in death of 5 patients. Rejection and uremia was cause of death in another 3 patients. One patient had rejection and liver failure. 2 patients died of hepatic coma, out of whom, one had fulminent acute hepatitis B. One patient died due to cardiac problem and another died of severe urogenital bleeding and shock probably due to renal infraction.

TABLE – 5

COMPLICATIONS IN TRANSPLANT PATIENTS

1.	Minor rejection episodes	14
2.	Rejection and loss of graft	09
3.	Recurrence of original disease	01
4.	Hepatitis	03
5.	Herpeszoster	06
6.	Hirsutism	03
7.	Renal artery stenosis	01
8.	Tuberculosis	05
9.	Diabetes millitis	01
10.	Hypertension	12
11.	Acid peptic disease	04
12.	Tinea versicolor infections	04
13.	Nephrotoxicity of cycloporine	20
14.	Peripheral vascular insufficiency	02
15.	Tremers	03
16.	Urinary tract infection	08
17.	Pneumonia	04
18.	Ureteric obstruction	01
19.	Septicaemia	05
20.	Mild hepatic dysfunction responding to decrease in cyclosporine.	03

TABLE – 6

CAUSES OF DEATH

1.	Cardiac	1
2.	Hepatic Coma	2
3.	Hepato cellular failure with sepsis	1
4.	Rejection with sepsis	5
5.	Rejection with uremia	3
6.	Urogenital bleeding with shock	1
7.	Liver failure + rejection	1

Table- 7 shows the causes for loss of grafts. Twelve grafts were lost due to rejections. Four patients died with functional grafts, were lost to rejections. Four patients died with functional grafts, one had renal artery stenosis and one had recurrence of focal segmental glomerulosclerosis in the graft.

In 46 patients who are alive with functional graft, mean serum creatinine level was 1.68 ± 0.78 mg/dl and mean blood urea level 48 ± 0.25 mg/dl. These patients are well rehabilitated and quality of life is acceptable.

TABLE – 7

CAUSES OF LOSS OF GRAFT

– Rejection.	12
– Death of patient	4
– Renal artery stenosis.	1
– Recurrence of disease.	1

COMMENTS

Availability of the kidney donors has been a worldwide problem. Only 15-20% recipients have volunteer related donors (1). The greatest potential donor source is the unrelated donors, ideally the cadaver donor. Live unrelated donors are rarely used because the results are not better than that of cadaver donor. (2, 3)

One hundred and two patients were reported to have renal transplantation from non-related living donors in 4 different centres in Brazil. Out of these 72 patients were follow up for one year, 18 died, thus giving a patient survival rate of 75% (4). In our study 12 patients out of these 44, who had grafts from living unrelated donors died. This gives an overall survival rate of 70% which is not significantly different from the above study. One year cumulative survival was 75% which is comparable to 45-70% which has been reported in the past for those from cadaver sources (5,6). In present series the cumulative patient survival at 18 months in live-related transplants was 93% and in live unrelated transplants 63%. Cummulative functional graft survival of 93% at 18 months was seen in live related transplants, and 54% in live unrelated transplants. Cumulative patient survival and functional graft survival rates for live related transplants in our series are significantly better than in live unrelated transplants.

Renal transplantation was not done in diabetic patients before 1966. But now diabetic patients are routinely accepted for transplantation in many countries. The results of renal transplantation in 629 diabetic patients from different transplant centers show a patient survival of 75% and the kidney survival of 70% in related kidneys and 50% patients survival and 35% cadaver kidney survival at three years. Reported survival for patients for the first year varied from 55-70% and range of functional graft survival was between 35-60%, when survival curves for cadaver donor kidney transplants were calculated (7). In our study there wwere only seven diabetic patients out of which five are alive with functional grafts having a cummulative survival rate for these is 71% at 16 months. The difference is not statistically significant.

Patient and graft survival rates after transplantation in elderly have been lower than those in youthful patients(8). There were 4 patients of less than 20 years and 5 older than 50 years. It is difficult to compare the results in these patients because of smaller number, but when the graft survival was compapared in patients in 3rd, 4th, and 5th decades where we had relatively larger number of patient survival rate appeared to be better in 3rd decade compared to 4th decade (73% Vs 65%) and the results in 4th decade were better than 5th decade (65% Vs 50%). But these differences were not statistically significant.

Several complications were noted in our patients. Most frequent was nephrotoxicity and decreased renal function due to cyclosporine. It was seen in 21 out of 51 cases (41%) who received cyclosporine, Renal insufficiency seen during cyclosporine drug nephrotoxicity is high output failure that tends to be associated with slower increase in serum creatinine than that seen during allograft rejection. Patients weight remains stable, fever is never seen(9). Nephrotoxicity was severe problem in the early days when cyclosporine was introduced. Nephrotoxicity was caused in more than 80% of the cases by too high a dose of cyclosporine. Lower serum creatinine levels are achieved by reducing the dose from 15 to as little as 4 mg/kg/days after 4 weeks (10).

Acute rejections is common during early post-transplant period. Condition is characterized by fever, allograft tenderness, swelling, decrease in urine output, rising blood urea and creatinine and hypertension. Renal arteriography, radioactive hippuran renogram diagnostic ultrsound, several immunological assays, aspiration cytology and renal biopsy may be helpful in confirmation of diagnosis. Acute cellular rejection usually can be reversed by transient administration of high doses of steroids. Minor rejection episodes were seen in 14 cases and major rejection episodes, resulting in loss of graft, occured in 9 cases in this study. Several glomerular lesions develop in a high proportion of renal grafts functional beyond 6 months

Recurrence of the recipients original disease in transplant kidney has been reported in membranoproliferative glomerulonephritis Goodpasture syndrome, focal segmental glomeruloscrosis, sclerderma. Henoch schonlein purpura amyloidosis, membranous nephropathy and Berger's disease. Incidence of graft loss from recurrence of disease in first 4 diseases has been reported to be 10-30% (11). In this study one graft was lost due to recurrence of focal segmental glomerulosclerosis.

Twelve recipients who were not hypertensive, developed hypertension after successful renal transplantation. Several etiilogical factors have been implicated (a) renin dependent hypertension secondary to intrarenal ischaemia due to acute or chronic rejection, (b) transplant artery stenosis, (c) hypercalcemia (d) steriod therapy, (e) retention of host native kidney (12).

Liver dysfunction occurs in 15-40 perscent of transplant patients (12). This may be due to viral hepatitis or due to drugs. Acute viral hepatitis has been attributed to hepatitis A or B viruses, non A, non b, cytomeglovirus, herpes simplex virus. In this study one patient had fulmenent hepatitis B, and died in hepatic coma. In other two patients, who developed hepatitis and died because of liver failure, HBs Ag was negative. Liver dysfunction could also be due to drugs. Azathioprine has been incriminated as hepatotoxic. Alpha methyl dopa may also cause liver disease. Cyclosporine is well known to cause liver dysfunction. White has reported an incidence of 4 to 7% (14) Six percent of our cases developed elevated liver enzymes, serum bilirubin and alkaline phosphatase which responded to decrease in dose of cyclosporine.

Setroid diabetes is not an uncommon complication. It occurs in 5-10% of all renal transplant recipients (12). Most patients with steroid diabetes ultimately may not require insulin therapy. This type of diabetes is rerely complicated by keto-acidosis. We had one patient who developed diabetes following renal transplantation and is on insulin therapy for more than 3 years.

Cutaneous complications seen in our patients were herpes zoster in 6 patients tinea versicolar skin infection in 8 patients. Herpes zoster was seen in patients who were getting azathioprine, prednisolone and cyclosporine together. None of the patients who were on azathioprine and predisolone had this problem. Incidence of herpes zoster has been reported to be 13% in immunosuppressed patients. (13). Incidence of tinea versicolor in these patients is 18% compared to only 0.5% in normal individuals in temperate climate (13). Incidence of tinea versicolor infection was 13% and of herpes zoster 10% in our series. Denovo malignancies develop in 5.5% cases and average time of appearance of such tumours is 28 months. Lymphoma occur commonly. Reticulum sarcoma has high mortality rate (14). None of our cases has this complication.

Different surgical complications, urinary extravasation, ureteric stenosis, ureteral stone, lymphocoele, renal artery stenosis renal vein or ileal vein thrombosis, can occur in these patients. One patient in our series lost the kidney due to renal artery thrombosis. One patient underwent exploration for ureteric obstruction and had improved renal function after surgery. One patient had ileal vein thrombosis.

Sepsis is the major cause of morbidity and mortality (15). Infections in the post transplant period can be divided into bacterial, fungal, viral and protozoal. Urinary tract infection is the most common cause of bacterial sepsis among recipients of renal allografts. Gram negative bacteria are the most common organisms arising from the genitourinary system. Pulmonary infections have been an important cause of mortality among transplant recipients (16). Gram negative bactria, fungi pneumocystis carini and cytomegalovirus are common organisms. In this series, post transplant course was complicated by urinary tract infection in 8 cases, pneumonia in 4 cases while 5 patients developed pulomanary tuberclosis. In a recent report 46 of 450 renal transplant recipients developed tuberclosis after1-124 months of receiving the graft (17). Rifampicin, a chemotherapeutic agent, precipitates acute rejection episode by reducing bioavailability of the microsomal cytochrome P 450 system (9). In this study two patients had deterioration of renal allograft function when they were put on rifampicin. In one patient renal function improved by decreasing the dose of cyclosporine and in the Other case renal function improved after rifampicin was discontinued.

Interaction between erythrocin and cyclosporine has also been reported (18). Erythrocin has been shown to increase serum cyclosporine level. In this saries, two patients showed evidence of cyclosporine nephrotoxicity with addition of erythrocin. Kidney function decreased in these two patients when erythocin was started for sorethroat and became normal after erythrocin was discontinued.

Three different immunosuppressive regimens 1. Cyclosporine+Predisolone 2. Cyclosporine+Azathioprine and 3. Cyclosporine+Azathioprine and Prednisolone were used. Patient and functional graft survival in Cyclosporine+Prednisolone group was significantly better than Cyclosporine + Prednisolone + Azathioprine group. Survival in Azathioprine + Prednisolone group was not statistically different from the other two groups. The interpretation of these

results may not be correct because cyclosporine + prednisolone was used mainly in live related transplants while tripple therapy was used in live unrelated transplants.

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