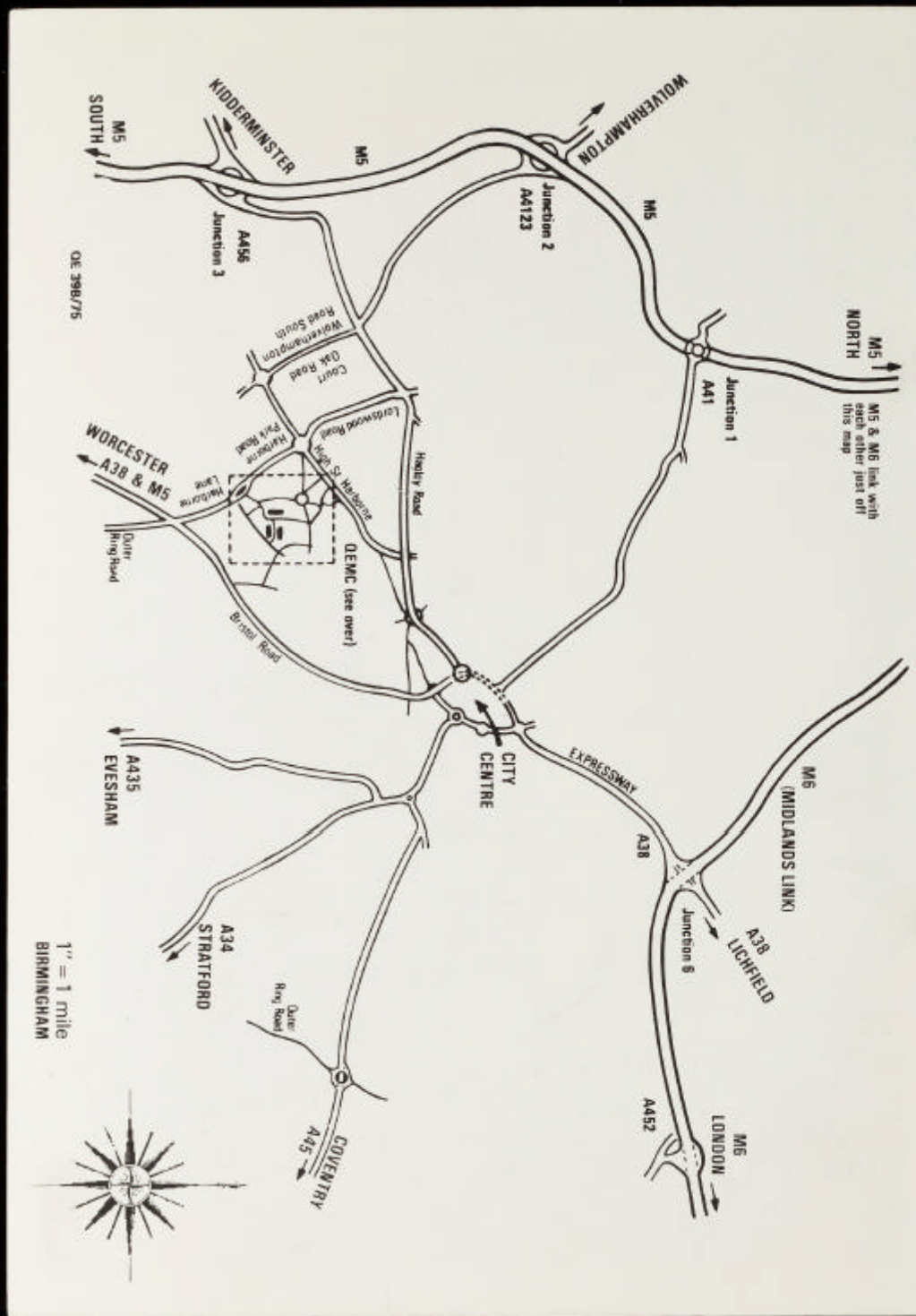

THE BRITISH TRANSPLANTATION SOCIETY

QUEEN ELIZABETH POSTGRADUATE
MEDICAL CENTRE, BIRMINGHAM

APRIL 8th and 9th, 1986

PAPER 1

DOES REGULAR MONITORING OF CYCLOSPORIN LEVELS HELP ?

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In order to evaluate monitoring of Cyclosporin (CyA) levels we have measured plasma trough levels 3 x weekly for 30 days after 31 consecutive renal transplants. Our objectives were, firstly to define the levels at which nephrotoxicity (NT) could be predicted and secondly, to determine whether a safe therapeutic range exists which minimises the chances of rejection and NT. Plasma CyA levels were performed by an HPLC technique and the clinical status of the graft was reviewed daily and defined by standard criteria for stable function, rejection, nephrotoxicity or ATN.

NT episodes occured in 7 patients, 4 of whom also had episodes of rejection CyA levels during NT (424 ± 62.2 ng/ml) were significantly higher than in those with stable function (216.3 ± 10 ng/ml) ($p \leqslant 0.001$). The mean CyA levels over 7 or 14 days of treatment were higher with NT than with stable function or rejection (Table).

Nineteen patients experienced rejection with 3 graft losses. The mean CyA level during rejection was 222 ± 13.2 ng/ml. There was no difference between the CyA levels of patients who lost their grafts (296 ± 33.1 ng/ml) and those whose rejections were successfully treated (224 ± 18 ng/ml).

It is concluded that regular monitoring does not define an effective range of plasma levels which minimises rejection or NT. However the mean CyA levels obtained over the first 14 days after transplantation may predict NT.

	Plasma CyA ng/ml (mean ± SEM)	
Events within 30 days	7 days	14 days
Uncomplicated	162·9 ± 19·3	168·5 ± 17·7
Rejection	175·1 ± 23·0	191·7 ± 24·6
Nephrotoxicity	286·0 ± 71·7	369·7 ± 75·1*
		Mann Whitney p = 0·05

PAPER 2

THE DIFFERENTIATION OF CYCLOSPORIN NEPHROTOXICITY AND ACUTE REJECTION BY URINE CYTOLOGY

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Differentiation between Cyclosporin nephrotoxicity and acute rejection is a major problem in renal transplant recipients. As Significant lymphocyturia is said to accur in acute rejection alone, we have cytologically examined the urine of renal transplant recipients to see whether lymphocyturia alone was diagnostic of rejection. Air-dried fixed smears of urine sediment in **55** events in 31 patients were stained by the Methyl green-Pyronin and Leishman technique and examined by high power light microscopy. Diagnosis was assigned blindly by retrospective analysis of clinical, biochemical and pathological parameters including Trucut biopsy, HPLC whole blood Cyclosporin levels, renal interstitial pressure measurements and response to treatment. **23**/**25** acute rejection episodes were associated with significant lymphocyturia ($\geqslant 2$/HPF), (sensitivity 92%, specificity 93%). 12/12 episodes of Cyclosporin toxicity alone showed no lymphocyturia. In an additional **16** non-rejecting cases (12 normal, 2 ATN, 1 severe UTI, 1 chest infection) there was no lymphocyturia. In 2 non-rejecting cases, one normal and one with severe polyarteritis nodosa, there was lymphocyturia. The absence of lymphocytes was thus 93% sensitive and 92% specific for non-rejection and 69% specific for Cyclosporin toxicity. The technique is potentially clinically useful in differentiating acute rejection from other causes of deteriorating renal allograft function. It is rapid, non-invasive and cheap, and can be performed in a ward side-room.

PAPER 3

CLASS II MHC EXPRESSION IN THE DIFFERENTIAL DIAGNOSIS OF CYCLOSPORIN A NEPHROTOXICITY IN CLINICAL RENAL TRANSPLANTATION.

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The differentiation of Cyclosporin A nephrotoxicity from acute rejection is a major problem in the management of renal transplant patients. Recently it has been demonstrated in the rat that cyclosporin A treated kidney allografts, in spite of a substantial cellular filtrate, do not show increased expression of class II MHC antigens. In contrast, substantial increases in class II MHC expression occurs in untreated rejection. Hence an evaluation of MHC class II antigen expression for the differential diagnosis of renal dysfunction in renal transplant patients was undertaken.

Nineteen needle biopsies from 16 patients were taken at times of renal dysfunction, and frozen sections were stained for class II MHC antigen expression using the immunoperoxidase technique and monomorphic mouse monoclonal antibodies. In 8 of the 16 patients, additional biopsies taken at or within 2 days of grafting were available for base-line comparisons. Diagnosis of cyclosporin A toxicity or rejection was made retrospectively on the basis of clinical and laboratory criteria. Scoring of the biopsies for class II expression was made without any knowledge of the patients' histories or clinical diagnoses.

Normal kidneys show no or only faint staining for class II antigens in cortical and medullary tubules. The level of staining in cortical tubular epithelial cells was taken as the measure of class II MHC expression. Eight of the nine biopsies taken during periods of dysfunction attributed to cyclosporin A toxicity had normal levels of class II expression. In contrast, nine of the ten biopsies taken during episodes of rejection had easily recognised increases in class II expression.

These results show that evaluation of class II MHC expression from biopsies clearly separates cyclosporin A nephrotoxicity from acute rejection. Moreover, biopsy results can be available within 1½-2 hours. The test is therefore likely to be of value in the correct diagnosis of the cause of renal dysfunction and thereby improve the management of cyclosporin A treated renal transplant patients.

PAPER 4

THE INFLUENCE OF IMMUNOSUPPRESSION ON INTRA-ORGAN PRESSURE MEASURED IN REJECTING HEART AND KIDNEY TRANSPLANTS

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Intra-organ pressure (IOP) has been noted to rise in rat heart and kidney allografts that are undergoing rejection. We wished to know if immunosuppression would abolish or delay this rise. Groups of 8-12 DA donor hearts or kidneys were transplanted to the neck or abdomen respectively of Lewis rats. Both the hearts and the kidneys were rejected by 7 days. IOP measured with a needle and manometer rose significantly ($p \leq 0.01$) from 28.6 ± 4 mmHg in hearts (27.4 ± 3 mmHg in kidneys) to 68.4 ± 3 (51.6 ± 9) mmHg by day 7. Cyclosporin i/m at a dose of 20 mg/kg/day completely suppressed rejection and IOP in the allografted hearts and kidneys remained in the normal range. 10 mg/kg/day of Cyclosporin was less effective allowing a temporary but significant rise in intramyocardial pressure on day 5, although no grafts were rejected. With 2 mg/kg of Cyclosporin all the cardiac allografts had raised myocardial pressures and half were rejected by day 16. All the kidney allografts survived although intrarenal pressures and creatinine levels remained significantly raised. The addition of methylprednisolone 16 mg/kg/ip on days 6 and 7 to low (2 mg/kg) Cyclosporin treatment had a striking effect. Raised myocardial pressures promptly returned to normal and all the cardiac allografts survived. Similarly intrarenal pressures and creatinine values were restored to normal in the rats with renal allografts. IOP values accurately reflected the effectiveness of immunosuppression, and in both heart and kidney allografts the pressure rose significantly when immunosuppression was reduced and fell when steroids were given.

PAPER 5

MAGNETIC RESONANCE IMAGING OF RENAL TRANSPLANTATION

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Magnetic Resonance Imaging uses the energy emitted from protons following external stimulation by a radiofrequency of known intensity. An image is built up from the signal which is dependent on the proton density, the NMR relaxation characteristics of the tissue, and any motion in the area being studied. To define the scope of NRI in the assessment of the renal transplant patient a pilot study of 30 investigations in 26 patients was carried out to identify the imaging conditions which would provide the most information about the transplanted kidney. Using a 0.15 Tesla resistive imager with a localised surface coil and a combination of IR 100, IR 700, and SE 80 sequences, we were able to demonstrate reduced cortico-medullary differentiation in acute rejection, a distended collecting system in obstruction, disturbances in blood supply and a perirenal haematoma. Examples of these abnormalities and of normally functioning renal transplants will be shown. Studies are now in progress to define the role of this investigation in the assessment of the renal transplant patient and to compare it with investigations currently in use.

PAPER 6

POST-OPERATIVE MORBIDITY AND MORTALITY OF LIVER TRANSPLANTATION

R.M. Kirby, P. McMaster, D. Clements, S.G. Hubscher, L. Angrisani, W.A.J. Jurewicz, D. Adams, J.A.C. Buckels, A.B. Jain, E. Elias.

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The main post-operative problems following liver transplantation have historically been technical complications, rejections and infection. Significant improvements in patient survival followed the introduction of Cyclosporin A in 1980. The current study was undertaken to see if these improvements resulted in less post-operative morbidity.

38 patients have been transplanted using Cyclosporin A, with 24 surviving. The thirty day hospital mortality was 27.8% and the actuarial 1 year survival was 56%. 8 patients required surgery in the post-operative period for bleeding (2), biliary leakage and obstruction (3) and duodenal perforation (1). 3 patients required surgery for removal of abdominal packs. Acute rejection occurred in 18 patients. Chronic rejection occurred in 4 patients, 3 of whom were retransplanted. All surviving patients had biliary bacterial contamination, but this progressed to cholangitis in only 6. Opportunistic fungal infection occured in 5 patients and 1 patient developed septicaemia. These patients, all of whom died, had other serious complications including large per-operative or post-operative blood loss (≥ 70 units) and renal failure. Chest complications, although common, (pleural effusions 26, collapse consolidation 17) were rarely a cause of serious morbidity in isolation. Although more than half of all patients undergoing liver transplantation will survive for more than one year, the post-operative period is still one of high morbidity and mortality.

PAPER 7

AUTOTRANSPLANTATION OF ISOLATED ISLETS OF LANGERHANS IN THE CYNOMOLGUS MONKEY

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We have recently described a method of isolation of islets of Langerhans from the human pancreas (1) and have now adapted the method to the cynomolgus monkey pancreas. The yield of islets obtained from 13 monkey pancreases was a mean 1319 islets per gram of pancreatic tissue (range 5333-1800) and the purity of the preparation varied from 5 to 15% islet tissue.

12 cynomolgus monkeys underwent total pancreatectomy, preparation of islets from the excised pancreas and autotransplantation to either the spleen or to the liver. 3 animals received no transplant and became immediately diabetic, surviving 4 to 8 days. 4 animals became normoglycaemic after intrasplenic islet transplantation, and survived 6 weeks, at which time splenectomy was performed with immediate onset of diabetes. Splenic vein insulin sampling confirmed the spleen as the source of insulin, and histological examination showed implanted islet tissue in all cases. 5 animals became normoglycaemic after intrahepatic islet implantation. 2 animals subsequently became diabetic at 4 and 5 months and 3 animals still have functioning grafts, the longest function being 9 months. These results suggest that sufficient islets can be extracted from a single donor pancreas to reverse diabetes.

(1) Diabetes 1984:33:1055-1061.

PAPER 8

HISTOLOGICAL APPEARANCES FOLLOWING RESCUE RETRANSPLANTATION OF REJECTING PANCREATIC ALLOGRAFTS

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An important factor in assessing the future viability of vascularised segmental pancreatic transplantation is the capacity of the graft to maintain effective endocrine structure and function following treatment of episodes of acute rejection. We have examined this in the rat by transplantation across a major histocompatibility barrier followed by graft retransplantation into the original strain. DA-DA-DA was the isograft retransplantation control, DA-Lew-DA the allograft rescue combination. DA-DA and DA-Lew transplants were examined concurrently. Streptozotocin rendered all recipients diabetic. Duct ligation was performed. Grafts were isolated intra-peritoneally with latex bags and retransplanted after 1-6 days. Pancreatectomy and histological examination were undertaken 2 weeks later. All 6 day allograft rescues failed. At 3 days exocrine cellular rejection was prominent and by 5 days severe, with an additional humoral component. Variable lymphocytic infiltration occurred in the islets. Duct ligation artefacts were extensive. Retransplanted 3 day allografts had reduced infiltrations with intact islets similar in appearance to comparable isografts. Extensive healing and fibrosis occurred in 5 day allografts, but more islets were disrupted with damaged beta cells.

In conclusion, some early changes of acute rejection appear reversible in this model, but a degree of irreversible islet damage had occurred at least 3 days before blood sugar elevation.

PAPER 9

URINARY AMYLASE AS A MARKER OF REJECTION IN DUCT TO URETER DRAINED PANCREAS GRAFTS

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Recent clinical experience in pancreas transplantation has shown that ductal drainage into the urinary tract is an effective method of managing the problem of exocrine secretions with the avoidance of fibrosis and ensuing endocrine damage which follows duct ablation. Changes in graft exocrine function can then also be measured with a view to monitoring rejection by changes in urinary amylase levels.

Iso and allograft pancreatic transplantation was performed in streptozotocin induced diabetic F1 (RTuxl) hybrid male rats using a cuff technique with duct to ureter anastomosis for exocrine drainage. The urinary amylase levels were monitored daily and correlated with serum amylase, insulin and glucose values. In isografted animals urine amylase values above 2,000,000 IU/24Hrs indicated stable graft function. In the allografted animals, urinary amylase values reached a peak around the fourth post-transplant day. A significant decline to pretransplant levels preceded the return of glycosuria and hyperglycaemia by a mean of 2.5 days.

We conclude that amylase secretion is an early sensitive indicator of pancreatic graft function and rejection. This data would also support histological evidence that rejection occurs earlier in the exocrine element of the grafted pancreas, than the islets of Langerhans.

PAPER 10

IMPOTENCE IN RENAL FAILURE

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Clive Glass — Department of Clinical Psychology, University of Liverpool.

Over 75% of men on dialysis are impotent. The causes include drugs, atherosclerosis, autonomic neuropathy (diabetes), hyperprolactinaemia and psychological problems. Many will improve after transplantation.

Twenty nine patients have been studied with hormone estimation, nucleide penography, nocturnal penile tumescence studies (NPT'S). Tumescence studies detect adequate erections during sleep indicating a probable psychological cause of impotence. Ten patients have been studied on dialysis, fourteen after transplantation and five both before and after transplantation. Twenty one patients have had NPT's. Of those fully evaluated, the diagnosis and result of treatment are as follows:

		On Dialysis	After Transplantation
Cause	psychological	5 }	5 }
	organic	3 } 8	5 } 10
Treatment			
	counselling	4	5
	other	3	3
	none/awating	1	2
Response	better	4	7
	no change	3	1

Four of the five patients investigated before and after transplantation improved spontaneously.

Ten patients were counselled because of psychological problems, eight were much improved. Other treatments consist of hormone treatment and penile prosthesis, three out of six have improved. If possible, irreversible causes of impotence should be diagnosed and treated prior to transplantation. However, counselling especially during a wait for a transplant is very valuable and may save threatened partnerships.

PAPER 11

THE AVAILABILITY OF ORGANS FOR TRANSPLANTATION: A THREE YEAR STUDY

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The records of all patients who died in the five intensive care units, covered by one transplant unit, were examined. The population in the district during the time of the study was 1.42 million. The latter six months of 1985 were examined concurrently and the previous 42 months retrospectively. All patients who were ventilated and diagnosed as brain stem dead, without gross sepsis or malignancy, were considered to be possible donors.

Results	Kidney donors and brain dead details			
	1983	1984	1985 —Jun	1985 —Dec
Donors used	16	21	10	6
Refused—relatives	1		4	7
coroner		1		
Not offered	19	16	4	2
Total possible donors	37	38	33	

This means that there are 51 possible kidneys/million/annum of which only 49% are used for transplantation.

Of the 108 patients who were possible donors in the three years 76 (18/million/annum) were possible liver donors and 15 (13/million/annum) were possible heart donors. The actual numbers of organs taken were five livers and 14 hearts.

In 1975 Dombey and Knapp in Nottingham recognised a possible 43 kidneys/million population in one year with 16 (37%) transplanted (1). Ten years later there has been some improvement (49% transplanted) but the full potential of cadaveric donation is yet to be realised. Alarmingly, in the concurrent study seven out of a possible 15 donations were recognised as refusal by relatives.

(1) Dombey, S. C., Knapp, M.S. Prospective survey of availability of cadaveric kidneys for transplantation.

Brit. Med. J. 1975 **2**: 482-483.

PAPER 12

SUBSTANTIAL BENEFITS OF HLA MATCHING IN KIDNEY TRANSPLANTATION

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There have been many reports of modest improvements in graft survival through HLA matching. We report a rigorous statistical analysis of 2282 first cadaveric kidney transplants recorded by the United Kingdom Transplant Service. HLA-matching has produced enormous improvements in survival for very well matched grafts, but only slight improvements have resulted from moderately good matching (Table). So far, few grafts have benefitted substantially from HLA matching, but simulations show that over 60% of grafts could be beneficially matched against a waiting list of 3000 patients. These results are reviewed in Cyclosporin treated patients and in retransplants.

Total HLA (A+B+DR) mismatches	% 1-year graft survival*	Relative risk†	p-value‡	Transplants	
0‡	93%	—	—	73	
1(on A)	86%	2·0	·07	108	beneficial
1(on B)	81%	2·7	·02	97	
1(on DR)	67%	5·2	·0001	96	
2	73%	4·1	·0005	603	
3	70%	4·7	·0001	720	non-beneficial
4	71%	4·5	·0002	399	
5	65%	5·7	·00003	154	
6	70%	4·7	·002	32	

*Estimated multifactorially, controlling for transplant centre and year of transplant.
† A relative risk is the daily rate of graft failure relative to zero A+B+DR mismatches.
‡ Significance of decrease in graft survival relative to zero A+B+DR mismatches.

PAPER 13

DOES MATCHING MATTER IN PATIENTS TREATED WITH CYCLOSPORIN A (CyA)?

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The importance of HLA matching and pre-transplant blood transfusions (PTF) for renal transplant patients treated with CyA is still the subject of debate. We present here an update of our single centre study of 337 patients, 191 treated with CyA and 146 treated with Azathioprine and Prednisolone (Aza). Only patients on whom full HLA matching was available were included and patients dying with a functioning graft were withdrawn at the time of death.

Our results show that for patients receiving Aza, graft survival decreased with increase in number of mismatches (MM) at HLA A, B or DR, the strongest effect being seen for HLA B. No effect of PTF or recipient sex was seen. For patients on CyA no benefit of close matching at HLA A, B or DR was seen. PTF were deleterious and female recipients had a 20% better graft survival rate than did males.

12 MONTH GRAFT SURVIVAL RATES

		CyA	N	Aza	N
HLA DR	— 0MM	69·22	73	65·66	38
	1MM	67·05	88	50·73	72
	2MM	89·47	30	41·20	36
HLA A	— 0MM	63·95	50	58·82	53
	1MM	72·86	100	53·85	74
	2MM	76·71	41	31·44	19
HLA B	— 0MM	74·29	34	75·12	33
	1MM	70·10	99	51·46	83
	2MM	73·83	58	31·13	30
MALE		63·67	132	51·86	104
FEMALE		87·64	59	55·04	42
OPTF		87·94	36	53·83	26
> OPTF		67·12	104	56·60	69

PAPER 14

ERYTHROCYTE MISMATCHES DO NOT APPEAR TO AFFECT KIDNEY GRAFT SURVIVAL

B.A. Bradley, P. Johnson, W.R. Gilks, S.M. Gore on behalf of the UKTS users.

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There are no comprehensive studies of the role of erythrocyte antigen mismatches in renal allograft survival. In 1980 a multicentre collaborative study was initiated by the UK Transplant Service to investigate this. 10,000— Blood/spleen samples were typed for antigens of the ABO, Rhesus, MNSs, P, Lutheren, Lewis, Duffy, Kidd and Kell systems in a single laboratory with a common set of reagents. A microtitre method was used throughout. Typing results were frequently checked with repeat samples and careful note was taken of recent blood transfusions. In over 3000 samples the effect of recent transfusions was investigated and found to be an important source of error in determining the phenotype, changing up or down the frequency of certain antigens. In general this was reflected in an increase in heterozygous phenotypes. Graft survival was examined at 15, 40 and 90 days post-op., in 1126 first cadaveric transplants; univariate analysis show that individual erythrocyte mismatches do not significantly affect graft survival.

PAPER 15

THREE YEAR EXPERIENCE OF DONOR SPECIFIC TRANSFUSION (DST) AND CONCOMITANT CYCLOSPORIN A (CYA)

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A prospective controlled randomised trial was started in 1983 to see if CyA would reduce the reported incidence of 30% sensitisation following DST. 46 patients with at least one haplotype mismatch and a reactive mixed lymphocyte culture were studied. All patients received 200 mls of fresh blood at 2 weekly intervals, 8 weeks before transplantation. 21 patients entered the treatment group and received CyA (10 mg/kg) from one week before DST. Transplantation was performed if T and B cell crossmatches were negative 4 weeks after the last DST. 6/25 patients given DST alone were sensitised, 1 transiently and 5 permanently. One patient had a positive crossmatch to his donor before DST which did not alter. 17 control patients were transplanted from their donor. One graft was lost to rejection, 1 to recurrent disease, both after 18 months. 5/21 patients given CyA and DST developed transient B cell antibodies lasting 8-12 weeks, were transplanted. The remaining 16 patients received their grafts as planned. There were 2 graft losses; one patient died of myocardial infarction with good renal function, 1 graft was lost to rejection during severe infection with CMV. Graft survival was 90% (n=26) in both groups 2 years post transplantation, plasma creatinine was 149 ± 18, 171 ± 19 umol/l in control and treated respectively. Conclusion: CyA appears to reduce the risk of sensitisation without prejudicing the blood transfusion effect or subsequent graft function.

PAPER 16

BLOOD TRANSFUSION (BT), HLA-DRW6, AND RESPONSE TO DNCB SKIN TEST

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The cell-mediated immunity of 460 long-term dialysis patients was tested using the DNCB test. Among the patients sensitised to DNCB prior to any BT 60% (95 of 159) were strong responders compared to 25% (74 of 301) of those sensitised to DNCB after one or more units of BT ($p \leqslant 0.0005$). HLA-DRW6 positive patients were significantly more likely to be strong responders (95%, 18 of 19) compared to HLA-DRW6 negative patients (54%, 58 of 117; $p \leqslant 0.01$, p value corrected for the number of HLA-DR antigens studied), but only when sensitised prior to BT. Serial DNCB testing revealed a rise in the mean score from 5.0 ± 3.7 to 6.8 ± 5.0 ($p \leqslant 0.005$) again only when patients were sensitised prior to BT. Finally the DNCB score had value in predicting subsequent graft survival especially when patients were sensitised following BT. These results provide further evidence that BT depresses the CMI, and support the concept that HLA-DRW6 is a marker of a strong CMI, but this may be modified by BT. The BT status has to be taken into account when interpreting DNCB scores in the prediction of graft survival.

PAPER 17

THE NEUROPATHIC BLADDER IN RENAL TRANSPLANTATION

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Alan Woolfenden — Department of Urology, Royal Liverpool Hospital.

Since 1979 ten patients with neuropathic bladders have been fully assessed prior to transplantation. Four patients have spina bifida, two pelvic trauma, one spinal tumour, one sacral agenesis, two unknown aetiology,

The neuropathic bladder can be suspected on clinical grounds but can only be assessed by urodynamic studies. The neuropathic bladder is unstable, hypertonic, acontractile with evidence of outflow and obstruction ureteric reflux.

Pre transplant management of the seven patients who were using their own bladders at the time of end stage renal failure included:

Division of distal sphincter — 3
Bladder neck incision (BN1) — 2
Bilateral nephrectomy for gross reflux — 4

Six of these patients have received renal transplants and all have satisfactory function although one patient required BN1 to correct outflow obstruction. One patient is awaiting transplantation.

Three further patients had urinary diversions in infancy and subsequently required renal transplantation. Bladder recycling was employed. Two patients have reused their bladders after transplantation and are satisfactory although one has occasional enuresis, and the other employs self catheterization. The proper evaluation and treatment of the neuropathic bladder prior to transplantation is essential. With appropriate treatment bladders may be reused after many years.

PAPER 18

SYMPTOMATIC RENAL OSTEODYSTROPHY (ROD) AFTER TRANSPLANTATION; TREATMENT WITH 1 (OH) VIT.D (1 OHD).

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Twenty one patients who developed bone pain with a raised alkaline phosphatase (AP) 114 ± 36 days post transplantation were treated with 1 OHD (1.5 ± 0.15 ug/day). Pain was confined to the lower limbs in 19 patients, 4 had objective signs of proximal muscle weakness and 2 were unable to walk 100m. Radiological examination showed ROD or skeletal demineralisation in 16 patients. Isotope bone scan in 8 showed no evidence of aseptic necrosis. Serum PTH was elevated in 8 patients but normal in 4. 20/21 patients improved symptomatically within 3 months and AP fell from 286 ± 80 IU to 190 ± 26 at 6 months and 121 ± 8 at 1 year. Biochemical effects of 1 OHD were assessed in 25 patients (17 symptomatic patients and 8 others) on 1 OHD post transplantation. Immunosuppressive therapy was CyA alone in 14 and Az/P in 11. Serum calcium (Ca) increased in all patients (2.64 ± 0.04 to 3.12 ± 0.07 mmol/l), calcium phosphorus product (CaP) in 24/25 patients (2.26 ± 0.01 to 3.82 ± 0.3 mmol/l), mean plasma creatinine (Cr) rose from 170.2 ± 14.8 to 206 ± 22.8 mmol/l but fell to 149.8 ± 10.8 on reduction/discontinuation 1 OHD. There was a stronger correlation between rise in Cr and CaP ($r=0.93$) than with Ca alone ($r=0.74$). Cr increased by $\geqslant 50$ umol/l in 11 patients, 10 of whom received CyA (CyA v Az/P X^2 $p \leqslant 0.01$). Dosage of 1 OHD, starting Cr, Cr clearance and Ca were comparable in patients on CyA or Az/P but mean PO4 was lower in Az/P treated patients (0.74 ± 0.05 mmol/l; c f 0.94 ± 0.05 mmol/l; $p \leqslant 0.02$).

Conclusion: 1 OHD is symptomatically effective in such patients but the dosage employed caused a reversible rise in CaP and Cr. Az/P offered relative protection to 1 OHD nephrotoxicity.

PAPER 19

A CONTROLLED TRIAL OF TRIPLE THERAPY IN RENAL TRANSPLANTATION

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Using Cyclosporin alone or with steroids, 25% of our patients have lost their cadaveric kidney transplants within one year. Triple therapy has been advocated as being more effective (1) so this immunosuppressive protocol has been tried in a controlled clinical trial. Fifty five recipients of cadaveric kidneys (45 first transplants and 10 retransplants) were randomised to receive Cyclosporin (8 mg/kg) alone or triple therapy consisting of Cyclosporin (8 mg/kg), Azathioprine (1-1.5 mg/kg) and Prednisolone (0.3 mg/kg). The triple therapy patients were converted to Azathioprine and Prednisolone after 3 months and all patients have been followed up for 6-16 months. The two groups were well matched as regard numbers (27 versus 28), sex, age, HLA mismatch, previous blood transfusions, previous transplants and dialysis treatment. Rejection episodes in the triple therapy group were significantly less common ($0.7 \pm .7$ v $1.3 \pm .9$ $p \leqslant .01$) and fewer kidneys were rejected (0 v 5). However, significantly more patients developed infectious complications (10 v 0 $p \leqslant .01$) and more patients died (6 v 1). Seventy eight per cent of the transplants in each group are currently functioning. In our hands triple therapy has not improved the results of cadaveric renal transplantation since the better control of rejection has been outweighed by an increased morbidity and mortality.

(1) Fries, D., et al. Transplant. Proc. 1985; 17: 1222-6.

PAPER 20

DEMONSTRATION OF AN EXTRA-RENAL MECHANISM IN SUSTAINED POST-DEOXYCORTICOSTERONE (DOC) HYPERTENSION

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Following renal transplantation sustained hypertension, despite bilateral host nephrectomy, may be attributable directly to the graft (eg renal artery stenosis or chronic rejection) or alternatively it may be due to extra-renal mechanisms. Using an animal model of hypertension we have investigated the possible role of extra-renal mechanisms in maintaining hypertension after successful renal transplantation and in the absence of graft rejection.

Hypertension was induced in male Lewis rats following unilateral nephrectomy by administering DOC (12.5 mg thrice weekly) and 1% Na Cl+0.2% KCl as drinking water for four weeks. Systolic blood pressure was measured using an indirect technique. Renal transplantation (with removal of host kidney(s)) was performed 10 weeks post-DOC and blood pressures recorded for 12 weeks after transplantation. Renal transplantation ($n=17$) between normotensive animals failed to alter recipient blood pressure. Normotensive animals ($n=5$) which received kidneys from hypertensive rats remained normotensive. Lastly, hypertensive rats ($n=8$) underwent renal transplantation from normotensive animals. Although this initially lowered blood pressure, (146 ± 5 mm Hg one week post transplant) there was a progressive rise in blood pressure subsequently and by six weeks the animals were markedly hypertensive (180 ± 13 mm Hg, $p \leqslant 0.001$).

This study suggests that extra-renal mechanisms, such as peripheral vascular reactivity, can maintain hypertension despite the presence of normal renal function and provides one explanation for failure of bilateral host nephrectomy to improve blood pressure control.

PAPER 21

VIRUS INFECTION AND AUTOLYMPHOCYTOTOXIC ANTIBODIES IN RENAL TRANSPLANTATION

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A positive crossmatch test in highly sensitised patients (HSPs) may be caused by autolymphocytotoxic antibodies (autoabs) which do not harm the graft. The stimulus to their development is unclear but they are encountered after renal transplantation and in patients with virus infections. We aimed to determine to what extent virus infection contributed to the development of autoabs in highly sensitised patients both before and after transplantation.

Of 33 HSPs with one serum available before and 2 after autoab development, 9 developed autoabs before and 24 after transplantation. The control group comprised patients who developed non-autoreactive lymphocytoxic antibodies. The 3 sera were assayed for mycoplasma, adenovirus, HSV, VZ and CMV by CFT, and recent infection indicated by a $\geq$4-fold rise in titre (virus+). The results (Table) show a significant correlation between a rise in viral titres and autoantibody development in the post-transplant group only.

	Pre-transplant			Post-transplant		
	virus+	virus—	total	virus+	virus—	total
Autoab	1	8	9	*15 (63%)	9	24
Control	1	8	9	4 (17%) (p 0·01)	20	24

*11/15 patients developed serological evidence of CMV infection

In conclusion autolymphocytotoxic antibody development in HSPs is unrelated to virus infection prior to transplantation but may be caused by virus infection in the majority of cases (63%) after transplantation.

PAPER 22

THE SOURCE OF CYTOMEGALOVIRUS INFECTION IN SEROPOSITIVE RENAL ALLOGRAFT RECIPIENTS IS FREQUENTLY THE DONOR KIDNEY

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Cytomegalovirus (CMV) infection is a major cause of morbidity and mortality in renal allograft recipients. The source of CMV infection in seronegative recipients has been shown to be the donor kidney. In seropositive recipients the source of virus could be either reactivation of the recipient's own virus, or reinfection with donor virus. We have recently demonstrated such reinfection of a seropositive recipient with CMV from donor kidney in a recipient pair with a single donor. In order to establish whether reactivation or reinfection represents the major source of CMV infection in seropositive recipients, we have used restriction enzyme analysis of the viral DNA to establish the origin of the virus excreted in 11 recipient pairs, each with a single kidney donor. Four of these pairs had CMV seronegative donors and CMV excretion was not detected in any of these recipients post transplantation. The remaining 7 recipients pairs all had seropositive donors, and all recipients excreted CMV post transplantation, irrespective of their pre-transplant serological status (11 seropositive, 3 seronegative). Furthermore when the viral DNA was analysed, in each pair studied, the same strain of CMV was excreted by both recipients indicating that the source of the virus was reinfection from the donor kidney. Thus our data suggest that reinfection with virus of donor origin is more common in seropositive recipients than reactivation of the recipient's own virus. These data have important implications for strategies to prevent CMV infection.

PAPER 23

TENDINITIS IN RENAL TRANSPLANT PATIENTS

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Tendinitis is a new clinical entity identified in 12 patients following transplantation after examination of 167 patients. Tendinitis was distinguished from spontaneous tendon rupture which was also seen in four other patients. Tendinitis was found in supraspinatus and calcaneal tendons. Before transplantation the plasma phosphorus was higher in patients with tendinitis compared to asymptomatic controls (2.1 ± 0.47, 1.5 ± 0.56 mmol/l, $p \leqslant 0.001$) as was the plasma alkaline phosphatase (163 ± 106, 113 ± 64 IU, $p \leqslant 0.05$). Plasma calcium was not significantly different. Patients with tendinitis were longer on dialysis than controls (46 ± 39, 24 ± 22 months, $p \leqslant 0.001$). Following transplantation the plasma calcium was significantly higher in the tendinitis patients (2.75 ± 0.4, 2.53 ± 0.3 mmol/l, $p \leqslant 0.001$). The cumulative prednisolone dosage was higher in patients with tendinitis at 1 month after transplantation (87 ± 46, 59 ± 31 mg/kg, $p \leqslant 0.025$) and also at 3 months (156 ± 111, 88 ± 56 mg/kg, $p \leqslant 0.005$). There was also a significantly higher number of patients with tendinitis receiving 1 OH Vit D (6/12 v 11/119, $X^2 = 11.14$, $p \leqslant 0.001$). No calcification was seen in the affected tendons on X-ray. Conclusion: Length of time on dialysis, hyperphosphataemia and a raised alkaline phosphate pre transplantation, hypercalcaemia cumulative prednisolone dosage and treatment with 1 OH vit D post transplantation appear to contribute to development of tendinitis.

PAPER 24

DOES 'ATN' HAVE AN ADVERSE EFFECT ON CYCLOSPORIN TREATED KIDNEYS?

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It has long been suggested that acute tubular necrosis (ATN) has an adverse effect on long term survival and function of kidney transplants. However, the diagnosis of 'ATN' has been applied to any patient with poor immediate renal function requiring post-operative dialysis (1). This has included patients whose kidneys have failed early from technical problems or accelerated rejection, so it has been difficult to know what the long term effects of genuine ATN might be. We have reviewed all our patients treated with Cyclosporin and have carefully identified and excluded those with technical failures and early accelerated rejection. In the remainder the influence of ATN has been examined. Over a three year period we transplanted 139 patients with immediate function and 43 patients in whom function was delayed. There were 21 patients whose transplants never functioned for reasons other than ATN. The functioning groups were well matched with regard to sex, age, blood transfusion, HLA A-B and DR mismatching and rejection episodes. Actuarial graft survival at 1 year was 88% for grafts exhibiting immediate function and 81% for those with 'ATN' (ns). Mean serum creatinine values (umol/l) were:—

	6 mths	9 mths	1 year	18 mths	2 years
Immediate function	168 ± 83	179 ± 94	182 ± 88	208 ± 121	190 ± 122
Delayed function	201 ± 82	228 ± 95	236 ± 116	229 ± 83	206 ± 78
Significance	$p < .05$	$p < .05$	NS	NS	NS

We would conclude that genuine ATN does not influence the survival of transplanted kidneys and except for the first nine months, transplant function is not significantly effected.

(1) S.I. Cho et al. Transplant. Proc. 1985; 17: 16.