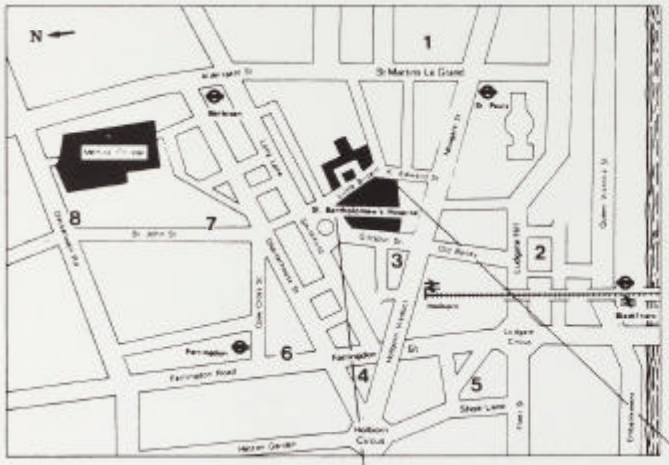
THE ROBIN BROOK CENTRE FOR MEDICAL EDUCATION
St Bartholomew's Hospital Medical College

Travelling Directions



BUS ROUTES

Serving stops shown on the map.

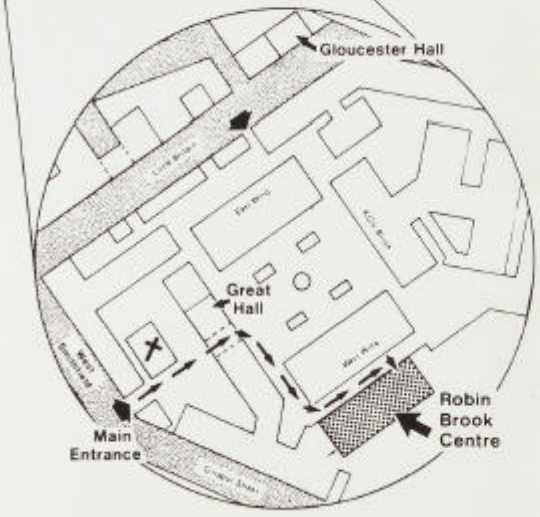
1. St. Martins le Grand - 4, 141, 502
2. Ludgate Hill - 4, 6, 7, 9, 11, 15, 18, 23, 141, 502, 513
3. Holborn Viaduct (Old Bailey) - 8, 22, 25, 501
4. Farringdon Street - 46, 45, 63
5. Shoe Lane - 4, 45, 46, 63, 77, 141
6. Farringdon Road - 63, 221, 259
7. Smithfield - 277, 279
8. Clerkenwell Road - 5, 55, 243

NEAREST B.R. STATIONS

Southern Region: BLACKFRIARS or HOLBORN VIADUCT

NEAREST UNDERGROUND

ST. PAUL's on the Central Line
FARRINGDON and BARBICAN on the Metropolitan and Circle Lines
BLACKFRIARS on the District and Circle Lines



PARKING FACILITIES

There is normally no parking within the Hospital precincts, though exceptions may be made at evenings and weekends. Access can be arranged for those with exhibition material or for caterers, to unload their equipment. Outside the hospital the following facilities are available:

NCP at Smithfield (not open at weekends)
NCP at Aldersgate Street (24 hours)
NCP at London Wall (Daytime)

Meters are suspended on Saturdays and after 6.30 pm in and around Smithfield Market and Charterhouse Square.

THE BRITISH TRANSPLANTATION SOCIETY

ST. BARTHOLOMEW'S HOSPITAL, LONDON
29TH OCTOBER, 1985

The Secretary reported that the Three Wise Men report would be published in the Lancet shortly and that the constitution of the Society was also being printed.

NEW MEMBERS

Margaret A. Forwell
George O'Sullivan
Naoshi Kamada
Carol A. Preistly
Richard D.M. Allen
Francis W. Ballardie
Michael G. Thick
A.B. Jain
Catherine Tate
A.R. Dennison
E.B. Bell
Spiros Drakopoulos
C.A. Gomes Da Costa
C.G. Koffman
Ann Stratton

7. Any other business

There being no other business the meeting was closed following thanks to the local meeting's secretary, Mr. Stuart Macpherson.

PAPER 1

THE KINETICS OF INDUCTION OF DONOR CLASS I AND CLASS II MHC ANTIGENS IN REJECTING HEART AND KIDNEY ALLOGRAFTS IN THE RAT

Andrew D. Milton, Sarah C. Spencer and John W. Fabre

Blond McIndoe Centre, Queen Victoria Hospital, East Grinstead, Sussex RH19 3DZ.

We have analysed in detail the kinetics of induction of donor MHC antigens during the rejection of heart and kidney allografts in the DA to PVG rat strain combination. The immunohistological and quantitative absorption techniques utilised monoclonal antibodies and assay systems specific for donor class I and class II MHC antigens.

Quantitative absorption analyses were performed on homogenates comprising 4-6 allografts pooled at each time interval examined (days 1 - 5 for kidneys, days 3 - 7 for hearts). In the heart allografts, donor class I antigen induction begins at day 3 when there is a modest (approximately 50%) increase in class I expression. Thereafter the induction proceeds rapidly. On the 4th and 5th post operative days the increase in class I expression compared to normal heart is approximately 4-fold and 7-fold respectively. The maximum level (a 10-fold increase) occurs at day 6, and thereafter the level declines, presumably because of myocardial necrosis. Donor class II antigen induction in the heart allografts follows a similar pattern to that just described for class I. In kidney allografts, it was of particular interest that donor class I induction occurred much more rapidly, being already evident on the first post operative day, and reaching levels 20-fold greater than normal kidney by day 3. Maximum levels (approximately 30-fold that of normal kidney) of donor class I antigens were reached on days 4 and 5. Donor class II induction, by contrast, developed in kidney grafts with similar kinetics to that seen for class II induction in heart grafts (beginning at day 3 and reaching a maximum of 7-fold over normal kidney at day 5).

Immunohistological studies were performed at days 1,3,5 and 7 after transplantation. These confirmed the timing of MHC antigen induction seen with the quantitative absorption analyses. By the fifth post-operative day, virtually all tissues in both heart and kidney grafts strongly expressed both class I and class II antigens, with the notable exception that class II antigens were not seen at any stage in the glomerulus.

PAPER 2

CELLULAR REQUIREMENTS FOR FIRST SET RENAL ALLOGRAFT REJECTION

E.M. Bolton, J.D. Briggs, J.A. Bradley

Department of Surgery and Renal Unit, Western Infirmary, Glasgow.

The roles played by cytotoxic T cells and T helper cells in allograft rejection are controversial. In this study, the cellular requirements for acute, first set, renal allograft rejection have been examined using an adoptive transfer model in the rat. Lewis ($RT1^l$) recipients of DA ($RT1^a$) strain kidneys rapidly rejected their grafts (MST 7, 6-8d) but sublethal whole body irradiation of recipients (750 or 850 rads) prevented graft rejection (MST>50 11 - 50d).

Reconstitution of irradiated recipients (850 rads) with 10^7 syngeneic, unsensitised lymph node cells restored graft rejection to near normal (MST 8, 7-9d). Lymphocyte subsets (5×10^6) prepared by rosette depletion using the monoclonal antibodies OX8 (anti-T cytotoxic/suppressor) or W3/25 (anti-T helper) were less effective than unseparated lymphocytes in restoring graft rejection (W3/25 depleted T cells, MST 14, 8-35d, OX8 depleted T cells, MST 24, 10-47d). In contrast to non-rejecting grafts from irradiated controls, rejecting grafts from animals reconstituted with either lymphocyte subset showed infiltration with many OX8 positive cells, raising the possibility that rejection following transfer of helper T cells may be mediated by host derived cytotoxic cells. Overall, however, these results emphasise the importance of contributions from lymphocytes of both cytotoxic and helper phenotype and suggest that both subsets are necessary for optimal first set renal allograft rejection.

PAPER 3

VASCULAR PROSTAGLANDIN SYNTHESIS DURING RENAL ALLOGRAFT REJECTION AND CYCLOSPORIN ADMINISTRATION IN THE RAT

C.P. Gibbons, K.N. Wiley, N.J. Lindsey, M. Fox, S. Beck, F.E. Preston, C.B. Brown, A.T. Raftery.

Urology/Transplantation Laboratory, Department of Pathology, Department of Haematology and Renal Transplant Unit, Royal Hallamshire Hospital, Sheffield.

Changes in vascular prostaglandin synthesis could mediate the decreased vascular perfusion and increased platelet deposition in acutely rejecting renal allografts and have been implicated in the possible vascular effects of cyclosporin.

Ex vivo prostacyclin and thromboxane A_2 synthesis were measured by radioimmunoassay of their stable products, 6 Keto $PGF_{1\alpha}$ and $T\alpha B_2$ in incubates of blood vessels taken from rats receiving renal allografts (DA to F_1 hybrid Agus x WAG) or isografts (DA to DA) and/or cyclosporin.

No consistent sustained change in 6 Keto $PGF_{1\alpha}$ production occured in the segment of donor aorta, renal artery or renal vein transplanted with the kidney or in the recipient aorta or IVC. $T\alpha B_2$ synthesis was significantly greater in allografted than isografted aortas and renal arteries from day 3 and in renal veins from day 5, but was not significantly different in the recipient aorta or IVC.

Cyclosporin (15mg/kg/day for 14 days or 100mg/kg/day for 7 days) did not affect vascular prostaglandin synthesis in ungrafted animals but (15mg/kg/day) reduced $T\alpha B_2$ production in allografted vessels to isograft values.

Vascular prostacyclin is unlikely to play a role in the mechanism of acute rejection and is unaffected by cyclosporin in the rat. Increased vascular thromboxane A_2 synthesis during acute rejection may be related to platelet deposition and could mediate changes in perfusion.

PAPER 4

QUANTITATIVE STUDIES OF THE SURVIVAL OF CRYOPRESERVED ISOLATED ADULT HUMAN PANCREATIC ISLETS OF LANGERHANS

D.W.R. Gray, G.W. Warnock, P. McShane, M. Peters and P.J. Morris.

Nuffield Dept. of Surgery, University of Oxford, John Radcliffe Hospital, Headington, Oxford OX3 9DU, England.

Although successful cryopreservation of isolated rat islets has been demonstrated there is no quantitative data available on human islet cryopreservation. Using a recently described technique (1) human islets of Langerhans were isolated from the pancreata of 13 adult organ donors, cultured, cryopreserved by a standard technique, stored at -196°C for 6-88 days, thawed and then cultured again. The number of islets recovered from an initial 200 was 160 ± 5 (S.E.M., 6 donors). The viability of cryopreserved islets was then compared with cultured islets from the same donor by implantation under the kidney capsule of nude rats. 15 nude rats were given xenografts of 200 cultured islets under the kidney capsule (from 13 donors) and a further 15 rats were given 200 cryopreserved islets similarly implanted (same 13 donors). Two weeks later tissue was visible at the site of implantation in all 30 rats. Histological examination of both groups showed the tissue to have the morphology of islets, confirmed by immunohistochemical localisation of insulin. The insulin content for kidneys bearing 200 cultured islets was 7.88 ± 1.6 mU (n=13) versus 6.84 ± 1.43 mU (n=) for kidneys bearing cryopreserved islets. We conclude that the techniques used for cryopreservation of isolated adult human islets in these studies enable a high recovery of tissue that survives after transplantation to nude rats.

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

PAPER 5

THE SYNERGISTIC EFFECT OF CYCLOSPORINE AND DONOR SPLEEN CELLS IN THE SUPPRESSION OF RAT RENAL ALLOGRAFTS

D. Cranston, K.J. Wood, P.J. Morris.

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Donor specific suppression of graft rejection by antigen pretreatment has been demonstrated in experimental models of transplantation, but its further elucidation is essential to a safe clinical application. In the rat, donor specific immunosuppression has been induced by pretreatment with whole cells and subcellular fractions. In the LEW ($RT1^l$) to DA ($RT1^a$) strain combination, we have previously induced indefinite renal allograft survival (MST>100 days) by pretreating recipients with 10^8 viable spleen lymphocytes seven days before transplantation. Pretreatment with 10^8 cells one day prior to transplantation was ineffective (MST 10 days). However 10^8 cells in combination with a three day course of 10mg/Kg/day of cyclosporine given on day -1,0 and +1 resulted in the induction of prolonged allograft survival (MST>100 days). Cyclosporine alone had no effect (MST 10 days). It would appear that cyclosporine and donor antigen on viable cells act synergistically. If the donor antigen stimulates a population of both suppressor and helper T cells, cyclosporine may act to ensure the predominance of the suppressor population thus favouring allograft survival.

PAPER 6

PLASMA EXCHANGE ALONE CAN PROLONG GRAFT SURVIVAL IN PRESENSITISED RATS

PAPER WITHDRAWN

N.J. Digard, K.R. Harris, P.R. Evans, J.L. Smith, M. Slapak.

Wessex Regional Transplant Unit, St. Mary's Hospital, Portsmouth.

The highly presensitised transplant recipient is becoming an increasing problem in many centres. In order to study possible ways of overcoming presensitisation we have developed a model of rat presensitisation to donor and plasma exchange (IPE) in a PVG to Wistar rat heterotopic cardiac allograft model.

Female Wistar rats were presensitised to PVG by skin grafting or by placement of donor heart fragments beneath the rectus sheath. Antidonor lymphocytotoxic antibody titres increased from 0 in proportion to sensitisation (1/64 - >1/1012). Plasma exchange was carried out on days -4, -3, -2 and -1 pre transplant to an equivalent daily exchange volume of 3 litres in man, and could be shown to remove 59.6 ±9.25% of a plasma marker daily, and reduce antibody titres from ≥1/64 to 1/16 over 4 exchanges.

Results of cardiac allografts are shown in the table.

Sensitisation and Treatment	Days of Graft Survival	MEAN ± SD	No. of	
Unsensitised Wistar	Control	8.2 ± 1.72	10	a
3 PVG Skin Grafts		0.83 ± 0.37	6	b
1 x rectus sensitisation	0.5,1.5,1.5,2.5,2.5,2.5,3.0,3.5	2.11 ± 0.87	8	c
1 x rectus sensitisation + IPE	4,4.5,4.5,5,6,6.5	5.08 ± 0.89	6	d
CyA 5 mg/kg + IPE	5,5,5.5,5.5,5.5	5.3 - 0.25	5	e
CyP 5 mg/kg + IPE	4,4,5,5,5	4.6 - 0.48	5	f

p a vs b < 0.01; a vs c < 0.01; a vs d < 0.01; d vs e ns; d vs f ns

In our hands plasma exchange alone, pre transplant, can prolong graft survival in a presensitised rat model. Preliminary data would indicate no additional beneficial effect from Cyclosporin A (CyA) or Cyclophosphamide (CyP).

PAPER 7

PHENOTYPIC ANALYSIS OF GRAFT INFILTRATING CELLS AND MHC EXPRESSION IN ACTIVELY ENHANCED RAT RENAL ALLOGRAFTS

I. McMillan, I. MacPhee, E.M. Bolton, J.A. Bradley.

Department of Surgery, Western Infirmary, Glasgow.

The mechanisms underlying the beneficial effect of blood transfusion on allograft survival are unclear. In the rat, administration of 1ml donor whole blood 7 days before renal transplantation produces indefinite graft survival in the AO ($RT1^{}$) to PVG ($RT1^{c}$) strain combination (MST increased from 10 to >50 days). Using this model, the morphology and phenotype of infiltrating mononuclear cells in rejecting, actively enhanced and syngeneic renal allografts, was examined. Grafts were removed on days 3, 5, 9 and 20 (enhanced and syngeneic) after transplantation and immunoperoxidase labelling using a range of monoclonal antibodies performed on both cryostat sections and on infiltrating cells extracted by enzyme digestion.

Paradoxically, blood transfusion failed to prevent the rapid and progressive accumulation of large numbers of mononuclear cells in the grafts. The pattern of infiltration and the morphology and phenotype of the infiltrating cells was similar in both rejecting and enhanced groups at days 3, 5 and 9, although a notable feature was the more rapid infiltration of enhanced grafts at day 3. Numerous infiltrating cells still resided in enhanced grafts 20 days after transplantation. By contrast, syngeneic grafts showed only a mild and transient infiltrate.

The cellular infiltrate in both rejecting and enhanced grafts was associated with the induction of class 1 MHC antigen expression on renal tubules, with no apparent difference between groups. Induction of class 11 antigen on tubules, which occurred earlier in enhanced grafts, appeared to be closely associated with the degree of cellular infiltrate, suggesting lymphokine release by graft infiltrating cells.

The absence of graft destruction despite heavy infiltration by cells phenotypically similar to those in rejecting grafts implies the existence of an immunoregulatory mechanism, possibly acting on the effector phase of the immune response in this model of active enhancement.

PAPER 8

PRESENTATION OF ALLOANTIGENS BY HOST CELLS

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*Department of Oral Immunology and Microbiology, Guy's Hospital Medical and Dental School, London.

Processing and presentation of protein antigens by accessory cells is a prerequisite for the induction of immune responses. We have shown that allogeneic histocompatibility antigens are handled similarly.

A cell transfer system was used. In typical experiments, $5 \times x\ 10^4$ BALB/c spleen cells were injected intraperitoneally (i.p.) into male CBA mice (primary hosts). Three days later spleen (SC) and peritoneal exudate (PEC) cells were harvested, depleted of T lymphocytes and administered i.p. to naive syngeneic CBA males. These secondary hosts were given BALB/c skin grafts 3 days after cell transfer. 5×10^7 SC or 3×10^6 PEC consistently caused accelerated rejection of the grafts.

This phenomenon is donor-specific, works in other strain combinations, and does not occur when T-depleted cells are transferred 10 days after activation of the 1^O hosts. It is therefore not due to the adoptive transfer of sensitivity by T lymphocytes. Rather, our evidence indicates that it is brought about by alloantigens processed and presented by accessory cells. Thus, the cells adhere to plastic, carry alloantigens and remain functional after paraformaldehyde treatment. Further, class I and class II, but not minor, histocompatibility antigens are involved in this transaction, and anti-host as well as anti-donor-Ia antibody blocks it.

Antigen presentation by host cells therefore occurs in the rejection of allogeneic skin grafts and in a system that is not MHC restricted.

PAPER 9

THE EFFECTS OF CYCLOSPORINE ON LYMPHOCYTE ACTIVATION IN A SYSTEMIC GRAFT-VERSUS-HOST REACTION

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*Department Immunology, Chelsea College, University of London, London.

We have investigated the effects of cyclosporine (CsA) on each of three stages of lymphocyte activation in vivo viz. sequestration of alloantigen-reactive lymphocytes from the circulation into the spleen and lymph nodes, blast transformation and induction of DNA synthesis in the activated cells and release of these cells and their progeny into the circulation. Parental strain lymphocytes-injected intravenously into semi-allogeneic rats recovered from the thoracic duct within 36 hours are profoundly unresponsive in a local GVH assay to the alloantigens of the F_1 hybrid but have normal activity against unrelated alloantigens (negative selection). CsA treatment of the F_1 hybrid recipients did not prevent this selective sequestration of antigen-reactive cells. In the untreated F_1 hybrid, from 36 hr after injection, large numbers of dividing blast cells were released into the lymph. These cells did not appear in the lymph of recipients treated with CsA. However CsA did not prevent the activation of cells sequestered in the spleen or lymph nodes as assessed by ^{3}H-thymidine incorporation and autoradiography. This unexpected finding suggests that CsA inhibits lymphocyte responses to alloantigens in vivo after DNA synthesis which is a later stage than the in vitro studies have shown.

PAPER 10

A COMPARISON OF THREE METHODS OF DETECTING EARLY KIDNEY TRANSPLANT REJECTION

J.R. Salaman, P.J.A. Griffin, C.A. Gomes Da Costa, D. Coughlin, K. Leach and D. Parry-Jones

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Since rejection can be difficult to detect in the early transplant period, particularly in the presence of acute tubular necrosis and Cyclosporin nephrotoxicity, we have prospectively examined the accuracy and usefulness of three physical tests in a sequential group of patients undergoing renal transplantation. These tests have been claimed to be able to diagnose rejection on the following basis:

Test	Main Rejection Indicators
1. Intrarenal Pressure (IRP)	Pressure > 40 mmHg
2. Tc-99 m DTPA Scan (TS)	Raised Perfusion Index. Reduced uptake (3 mins)
3. Ultrasound Scan (US)	>30% volume rise. ↑Sinus echoes. ↓C/M junction

Intrarenal pressure was measured using a fine needle and manometer. Ultrasound measurement of renal volume was performed using "Autocalc" ROM and verified on pre and post nephrectomy kidneys. The tests were carried out twice weekly (IRP) or weekly (TS, US) for three weeks. Patients were immunosuppressed with Cyclosporin and rejections have been reviewed retrospectively by an independent observer. Five hundred and nine tests have been analysed in 61 patients.

	NO REJECTION		REJECTION	
Tests (Total)	Total Tests	False Pos.Tests	Total Tests	False Neg.Tests
Intrarenal Pressure (227)	160	6 (3.8%)	67	6 (8.9%)
Isotope Scan (132)	106	7 (6.6%)	26	11 (42.3%)
Ultrasound Scan (150)	121	7 (5.8%)	29	16 (55.2%)

During periods of normal renal function or ATN all three tests gave few false positive results. During rejection however, approximately half of the isotope and ultrasound scans remained normal. The intrarenal pressure test was much more reliable with only 6 false negative results and we therefore conclude that of the three methods, measurement of intrarenal pressure was the most accurate in diagnosing rejection.

PAPER 11

PERFUSION OF HUMAN RENAL ALLOGRAFTS WITH THE ANTI LEUCOCYTE COMMON MONOCLONAL ANTIBODY, F10-89-4

D. Taube, K. Welsh, S. Snowden, M. Bewick

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Twelve cadaver allografts were perfused with anti leucocyte common (LC) monoclonal antibody as previously described before being transplanted into first time, non-sensitised recipients, five of whom were diabetic. Eighteen similar historical first cadaver allograft recipients served as controls. Post operatively, the patients and controls were similarly immunosuppressed with prednisolone and cyclosporin. Table 1 gives the details of their plasma creatinines and cyclosporin levels for the first three months post transplantation. One of our patients was transplanted with a kidney with five arteries and never functioned satisfactorily. Two other patients experienced mild reversible rejection episodes. Of the controls, two kidneys were lost as a result of rejection and nine other patients had a total of 15 reversible rejection episodes within three months. Our results, although very preliminary, suggest that perfusion with anti-LC may reduce the incidence of rejection and result not only in better graft survival but improved function.

Table 1

Time post Txp	Plasma creatinine (umol/l) ± 1 SD		Cyclosporin whole blood levels (ng/ml) ± SD	
	Patients	Controls	Patients	Controls
4 weeks	152 ± 64	251 ± 208	591 ± 227	568 ± 296
8 weeks	116 ± 19	229 ± 161	392 ± 116	407 ± 179
12 weeks	115 ± 33	226 ± 156	292 ± 138	343 ± 133

PAPER 12

HLA CLASS I AND CLASS II TISSUE MATCHING AFFECTS RENAL ALLOGRAFT LYMPHOCYTE INFILTRATION

R.F.M. Wood, D.L. McWhinnie, S.V. Fuggle and P.J. Morris

Nuffield Dept. of Surgery, University of Oxford, John Radcliffe Hospital, Oxford.

While the influence of HLA matching on graft survival is well recognized, its effect on T-lymphocyte infiltration of the graft is unknown. This relationship was examined in 103 biopsies obtained 8-40 days after transplantation from 70 patients receiving cyclosporine (Cy) or azathioprine/prednisolone (AP). T-lymphocyte populations were labelled in cryostat sections by monoclonal antibodies and immunoperoxidase staining. Infiltration was assessed by point counting and expressed as the percentage area of the section occupied by each T-lymphocyte component (±sem). Results were correlated with the number of donor/recipient mismatches.

	CLASS I MISMATCHES			CLASS II MISMATCHES		
T-Lymphocytes	0/1 v	3/4	P	0 v	2	P
AP-STABLE	2.4±0.5	6.5±1.0	<0.04	3.3±0.5	8.0±1.5	<0.01
AP-REJECTION	7.5±1.3	8.4±0.7	NS	8.8±1.0	10.3±1.0	NS
Cy-STABLE	3.2±0.8	2.3±0.5	NS	3.1±1.0	4.1±1.3	NS
Cy-REJECTION	2.6±0.6	6.8±0.9	<0.02	3.8±0.7	3.6±0.9	NS

Statistical Analysis — Mann-Whitney U-test

AP THERAPY. In stable function, T-lymphocyte infiltration increased with Class I and II mismatching. T-cell subgroup analysis showed that $T8^+$ infiltration increased only with Class I mismatching whereas $T4^+$ infiltration increased only with Class II mismatching. No effect was seen in rejection where overwhelming numbers of cells may have obscured the effect of tissue matching.

Cy THERAPY. In rejection the marked increase in T-lymphocyte infiltration with poor Class I matching was reflected in $T8^+$ but not $T4^+$ infiltration. In stable function, a matching effect was not seen perhaps due to effective suppression of infiltration by Cy.

CONCLUSIONS. Tissue matching affects:
1. the degree of T-cell infiltration. 2. the phenotype of infiltrating T-lymphocytes.

PAPER 13

THE EUROTRANSPLANT EXPERIENCE WITH CYCLOSPORIN A

G.F.J. Hendriks, P. de Lange*, G.M.Th. Schreuder*, J. D'Amaro*, G.G. Persijn, B. Cohen and J.J. van Rood*

Eurotransplant Foundation, Leiden, The Netherlands
*Dept. of Immunohaematology, University Hospital, Leiden, The Netherlands.

Since January 1981, the majority of the transplant centers in Eurotransplant have switched their immunosuppressive therapy from Prednison/Immuran to Cyclosporin A. 85% of the patients transplanted in 1984 received Cyclosporin A versus only 6% in 1981. In the transplants performed between 1981 and 1984, the one-year graft survival of unrelated first kidney grafts is 83% in the CyA group (n=1962), versus 66% in the non-CyA group (n=2290). The excellent results obtained in the CyA treated patients makes us wonder whether HLA-matching still improves graft survival and whether this HLA-matching effect still depends on the DRw6 status of donors and recipients. The answer to both questions is yes. In 336 DRw6- positive recipients of DRw6 positive grafts who received CyA, the graft survival at 1 and 2 years is 86% and 83%. 76 DRw6 positive recipients of DRw6 negative grafts showed a survival at 1 and 2 years of 72% and 56%. This difference in graft survival is highly significant (p=0.004). Thus DRw6 positive recipients should receive DRw6 positive grafts, whether or not CyA is given. The survival of DRw6 positive grafts in 196 DRw6 negative recipients, who received CyA, at 1 and 2 years is 85% and 79%. This so called "DRw6 effect" is independent of the cold ischemia time. In the group of 1332 DRw6 negative recipients of DRw6 negative grafts, the best result is obtained in the HLA-A,B and HLA-DR identical group (90% at 1 year, n=99). The interaction between DRw6 and HLA-matching is also observed in the non CyA group transplanted between 1981 and 1984 (data not shown). The Eurotransplant follow up data of living related transplants again clearly show this DRw6 effect in a group of 88 one haplotype shared donor/recipient pairs. The survival of DRw6 positive grafts (n=65) was 90% at 1 and 2 years in the DRw6 positive and DRw6 negative recipients versus 81% and 74% in 23 DRw6 positive recipients of DRw6 negative grafts. Our results led us to suggest that it is imperative, even in this era of Cyclosporin A therapy, that DRw6 positive patients receive a graft from DRw6 positive donors and that DRw6 negative patients are HLA A,B and Dr matched.

PAPER 14

QUADRUPLE THERAPY AFTER CADAVERIC RENAL TRANSPLANTATION USING KIDNEYS WITH PROLONGED COLD ISCHAEMIC TIMES (CIT)

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Wessex Regional Transplant Unit, St. Mary's Hospital, Portsmouth.

9 patients received RATG (Fresenius) at 3 mg/kg body weight for not longer than 8 days, in addition to Azathioprine 1 mg/kg body weight and Prednisolone 15 mgs daily. After discontinuation of RATG, Cyclosporin A (CyA) 12 mg/kg body weight was introduced, reducing to 3 mg/kg after one month.

Transplantation was performed using cadaveric kidneys with CIT of longer than 50 hours. ATG was only substituted for CyA in the triple therapy regimen previously published when urine volumes were less than 300 ml in the first 12 hours post-transplant. In 4 of the 9 patients transplants were performed across the ABO barrier. Mean mismatching at HLA A and B was 3.4 and DR 1.3. All 9 patients are surviving with a functional graft at the time of writing, 2 - 9 months after transplantation.

CONCLUSION: The use of ATG and the consequent avoidence of the early use of CyA in kidneys which have sustained ischaemic damage has, in the short term, given acceptable results. There has not been any evidence of lymphoma or undue viral infection, either in this group of patients or in the total group of 86 patients who have received either triple or, as pertains to the above 9 cases, quadruple immunosuppressive therapy.

PAPER 15

TRIPLE IMMUNOSUPPRESSION IN RENAL TRANSPLANTATION — INITIAL EXEPERIENCE

R.D. Allen, J.R. Chapman, P.J. Morris

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Although Cyclosporine (Cy) has improved renal allograft survival, whether used with or without steroids, its side effects and particularly the nephrotoxicity are a major concern. This has prompted us to perform a pilot study of triple immunosuppression using Cyclosporine (10 mg/kg), azathioprine (1.5 mg/kg) and prednisolone (20 mg). Our initial experience with 24 consecutive cadaver renal transplants is compared here with our previous experience of 64 patients treated with Cyclosporine alone at the higher dose of 17.5 mg/kg reducing to 12.5 mg/kg by 3 months.

Primary non-function of grafts with triple therapy (8%) was considerably better than with Cy alone (50%). 83% of patients treated with Cy, but only 54% of the triple therapy group, suffered an acute rejection episode within the first month. However 9% of Acute rejection episodes have led to loss of the graft in both groups.

Our major concern with triple therapy was that it might lead to increased infection, however this has not yet materialised. 38% on triple therapy have had UTI's compared with 52% using Cy, 20% compared with 17% had herpetic lesions, and 20% versus 19% suffered clinical CMV infection.

While the short follow-up and small number of patients urge continued caution, further evaluation of triple therapy is warranted.

PAPER 16

CYCLOSPORIN USE IN "HIGH RISK" CADAVERIC RENAL TRANSPLANT RECIPIENTS: IS LATE CONVERSION TO AZATHIOPRINE AND PREDNISOLONE SAFE?

T.W.J. Lennard, M. Venning, P.K. Donnelly, R.G. Wilson, G.W. Elliott, M.K. Ward, R. Wilkinson, J.R. Farndon, G. Proud, R.M.R. Taylor

The Renal Transplant Unit, Departments of Surgery and Medicine, Northern Region, Newcastle upon Tyne.

Since October 1983, Cyclosporin A (CyA) has been used as the primary immunosuppressive agent in patients at high risk of graft rejection (second or subsequent transplant; blood group match alone in priority patients) with conversion to Azathioprine and Prednisolone (A+P) at six months. 37 patients received CyA and were followed for 7-20 months. Concurrently, 46 patients received HLA B Locus matched kidneys with A+P as primary immunosuppression.

Graft survival to date is 81% in the CyA group and 70% in the A+P group. 23 patients were converted to A+P. One month later 20 had improved renal function. Two patient had a transient rise in plasma creatinine and two patients developed acute reversible rejection at 3 and 8 weeks respectively.

Mean plasma creatinine ± S.D. before and 1 month after successful conversion was 186 ± 79 and 153 ± 55 respectively (paired T test, $p<0.01$).

Mean current plasma creatinine ± S.D. in the converted and A+P groups is 147 ±54 and 129 ± 50 respectively ($p=0.1$ (N.S.)).

In summary:

1) Conversion from CyA to A+P was associated with no graft loss.
2) In most cases, conversion was uneventful and graft function improved.

We conclude that a policy of conversion from CyA to A+P at 6 months in high risk patients is safe.

PAPER 17

Ig CLASS AND SPECIFICITY OF ANTIBODIES CAUSING A POSITIVE T CELL CROSSMATCH: CORRELATION WITH RENAL ALLOGRAFT SURVIVAL

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Two techniques were used to investigate the Ig class and specificity of antibodies causing a positive T cell crossmatch in 25 cadaver and 4 living related donor grafts. 1. Sera were digested with dithiothreitol (DTT) which removes cytotoxicity due to IgM antibody. 2. Cytotoxicity of HLA class I (ABC) antibodies was blocked by preincubation of the target cells with PA2.6, a monoclonal antibody recognising an HLA-ABC monomorphic determinant. The results of the donor crossmatches after these treatments are shown in the Table.

Crossmatch results		Inferred class and specificity	No.	Grafts functioning at 3 months
DTT digested	Not blocked	IgM, non-HLA	17	15 (88%)
DTT digested	Blocked	IgM, HLA-non	7	6 (86%)
Not DTT digested	Blocked	IgG, HLA-non	5	0 (0%)

The sera of all 17 patients with IgM non-HLA antibodies were autoreactive and good graft survival (88%) was seen. In the remaining 12 patients the positive crossmatches were blocked by PA2.6 suggesting the presence of HLA-ABC antibodies. In 7 patients the antibody was DTT digested, indicating an IgM antibody, and 6 grafts (86%) were functioning at 3 months. by contrast in the 5 patients whose antibody was not DTT digested (IgG) no grfts functioned. This preliminary study suggests that IgG HLA-ABC antibodies are harmful whereas IgM antibodies are not.