THE BRITISH TRANSPLANTATION SOCIETY

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

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. Martin le Grand - 4, 141, 502
2. Ludgate Hill - 4, 6, 7, 9, 11, 15, 16, 23, 141, 502, 513
3. Holborn Viaduct (Old Bailey) - 8, 22, 25, 501
4. Farringdon Street - 49, 45, 67
5. Shoe Lane - 4, 45, 46, 63, 77, 141
6. Farringdon Road - 63, 221, 259
7. Smithfield - 271, 279
8. Clerkenwell Road - 3, 55, 243

Nearest B.R. Stations
Southern Region: BLACKFRIARS or HOLBORN VIADUCT

Nearest Underground
ST. PAUL’S on the Central Line
FARRINGDON and BARRICAN on the Metropolitan and Circle Lines
BLACKFRIARS on the District and Circle Lines

Parking Facilities
There is 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 (Dartine)
Meters are suspended on Saturdays and after 6:30 pm in and around Smithfield Market and Charterhouse Square.
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. Farrow
George O'Sullivan
Naoshi Kamada
Carol A. Priestly
Richard D.M. Allen
Francis W. Ballard
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
Bond 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 1/6 allografts pooled at each time interval examined (days 1, 5 for kidneys, days 3, 7 for hearts). The induction of class I antigen 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 5-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.
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\(^a\)) recipients of DA (RT1\(^d\)) strain kidneys rapidly rejected their grafts (MST 7, 5-8d) but sublethal whole body irradiation of recipients (750 or 850 rad) prevented graft rejection (MST>50 11 - 50d).

Reconstitution of irradiated recipients (850 rad) with 10\(^7\) syngeneic, unprimed lymph node cells restored graft rejection to near normal (MST 8, 7-9d). Lymphocyte subsets (5 x 10\(^5\)) 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, 16-47d). 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


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 radiomunoassay of their stable products, 6Keto PGF\(_{1\alpha}\) and TXB\(_2\), 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 6Keto PGF\(_{1\alpha}\) production occurred in the segment of donor aorta, renal artery or renal vein transplanted with the kidney or in the recipient aorta or IVC. TxB\(_2\) 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 TxB\(_2\) 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.
QUANTITATIVE STUDIES OF THE SURVIVAL OF CRYOPRESERVED ISOLATED ADULT HUMAN PANCREATIC ISLETS OF LANGERHANS


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 pancreas 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=7) 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.

PLASMA EXCHANGE ALONE CAN PROLONG GRAFT SURVIVAL IN PRESENSITISED RATS

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 sensitised to PVG by skin grafting or by placement of donor heart fragments beneath the rectus sheath. Antitumor lymphocytotoxic antibody titres increased from 0 in proportion to sensitisation (1/64 > 1/1024). Plasma exchange was carried out on days 4, 12 and 1 post 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 1/94 to 1/16 over 4 exchanges.

Results of cardiac allografts are shown in the table.

<table>
<thead>
<tr>
<th>Sensitisation and Treatment</th>
<th>Days of Graft Survival</th>
<th>MEAN ± SD</th>
<th>No. of</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Unsensitised Wistar 3 PVG Skin Grafts</td>
<td>Control</td>
<td>8.2 ± 1.72</td>
<td>10</td>
<td>a</td>
</tr>
<tr>
<td>1 x recess sensitisation</td>
<td>0.5,1.5,2.5,3.2,3,2.5,3,0.5</td>
<td>2.11 ± 0.87</td>
<td>8</td>
<td>c</td>
</tr>
<tr>
<td>1 x recess sensitisation + IPE</td>
<td>4.4,4,5,5,6,5</td>
<td>5.08 ± 0.91</td>
<td>6</td>
<td>d</td>
</tr>
<tr>
<td>CyA 10 mg/kg + IPE</td>
<td>5.5,5,5,5,5,5,5</td>
<td>5.3 ± 0.25</td>
<td>5</td>
<td>e</td>
</tr>
<tr>
<td>CyP 5 mg/kg + IPE</td>
<td>4.4,4,5,5,5</td>
<td>4.6 ± 0.48</td>
<td>5</td>
<td>f</td>
</tr>
</tbody>
</table>

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).

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

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 i.v. donor whole blood 7 days before renal transplantation produces indefinite graft survival in the AO (RT1.) to PVG (RT1.) 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 that seen 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 I MHC antigen expression on renal tubules, with no apparent difference between groups. Induction of class II 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

Rosemary A. Sherwood, Leslie Brent and Lee S. Rayfield*

Department of Immunology, St. Mary's Hospital Medical School, London
*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, $5 \times 10^4$ 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. $5 \times 10^4$ SC or $3 \times 10^4$ 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 10 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 allogeneic 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 IgM 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


Department Immunology, Manchester University Medical School, Manchester
*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. Parenteral 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 F1 hybrid but have normal activity against unrelated alloantigens (negative selection). CsA treatment of the F1 hybrid recipients did not prevent this selective sequestration of antigen-reactive cells. In the untreated F1 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 3H-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.
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
Department of Transplantation Surgery, Royal Infirmary, Cardiff.

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:

<table>
<thead>
<tr>
<th>Test</th>
<th>Main Rejection Indicators</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Intrarenal Pressure (IRP)</td>
<td>Pressure &gt; 40 mmHg</td>
</tr>
<tr>
<td>2. Tc-99m DTPA Scan (TS)</td>
<td>Raised Perfusion Index, Reduced uptake (3 mins)</td>
</tr>
<tr>
<td>3. Ultrasound Scan (US)</td>
<td>x 50% volume rise, * Sinus echoes, 4C/M junction</td>
</tr>
</tbody>
</table>

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.

### Table 1

<table>
<thead>
<tr>
<th>Time post Txp</th>
<th>Plasma creatinine (umol/l)</th>
<th>Cyclosporin whole blood levels (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients ± 1 SD</td>
<td>Controls ± 1 SD</td>
</tr>
<tr>
<td>4 weeks</td>
<td>152 ± 64</td>
<td>251 ± 208</td>
</tr>
<tr>
<td>8 weeks</td>
<td>116 ± 19</td>
<td>229 ± 161</td>
</tr>
<tr>
<td>12 weeks</td>
<td>118 ± 33</td>
<td>226 ± 156</td>
</tr>
</tbody>
</table>

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

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 108 biopsies obtained 8-40 days after transplantation from 70 patients receiving cyclosporin (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 (%sm). Results were correlated with the number of donor/recipient mismatches.

<table>
<thead>
<tr>
<th>CLASS I MISMATCHES</th>
<th>CLASS II MISMATCHES</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-Lymphocytes</td>
<td></td>
</tr>
</tbody>
</table>
| 0/1                | 2/3                | P    | 0/1     | 2      | P
| AP STABLE          | 24.0±1.5           | 6.5±1.0 | <0.01 | 3.3±1.5 | 80/1.1 | <0.01 |
| AP REJECTION       | 7.5±1.3            | 8.4±0.7 | NS    | 8.8±1.0 | 10.5±1.0 | NS    |
| CY STABLE          | 3.2±0.6            | 2.3±0.3 | NS    | 3.1±1.0 | 4.1±1.3 | NS    |
| CY REJECTION       | 26.0±0.6           | 6.8±0.9 | <0.02 | 3.8±0.7 | 38.0±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

THE EUROTRANSPLANT EXPERIENCE WITH CYCLOSPORIN A

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 Prednisol/Immunog 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 affects graft survival and whether this HLA matching effect still depends on the DR6 status of donors and recipients. The answer to both questions is yes. In 336 DR6+ positive recipients of DR6+ positive grafts who received CyA, the graft survival at 1 and 2 years is 86% and 83%. 36 DR6+ positive recipients of DR6- negative grafts showed a survival at 1 and 2 years of 72% and 53%. This difference in graft survival is highly significant (p<0.001). Thus DR6+ positive recipients should receive DR6+ positive grafts, whether or not CyA is given. The survival of DR6- positive grafts in 196 DR6- negative recipients who received CyA at 1 and 2 years is 85% and 79%. This so-called "DR6 effect" is independent of the cold ischemia time. In the group of 1332 DR6- negative recipients of DR6- 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 DR6 and HLA matching is also observed in the non-CyA group transplanted between 1981 and 1984 (not shown). The Eurotransplant follow up data of living related transplants again clearly show this DR6 effect in a group of 88 one haplotype shared donor/recipient pairs. The survival of DR6+ positive grafts (n=65) was 90% at 1 and 2 years in the DR6+ positive and DR6- negative recipients versus 81% and 74% in 23 DR6- positive recipients of DR6- negative grafts. Our results lead us to suggest that it is imperative, even in this era of Cyclosporin A therapy, that DR6+ positive patients receive a graft from DR6+ positive donors and that DR6- negative patients are HLA A,B and DR matched.
QUADRUPLE THERAPY AFTER CADAVERIC RENAL TRANSPLANTATION USING KIDNEYS WITH PROLONGED COLD ISCHAEMIC TIMES (CIT)

M. Slapak, N. Digard, C. Gosling, K. Ahmed, D.G. Querci, R. Crockett
International Kidney Organisation, Southsea, Hants.
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 avoidance 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.

TRIPLE IMMUNOSUPPRESSION IN RENAL TRANSPLANTATION — INITIAL EXPERIENCE

R.D. Allen, J.R. Chapman, P.J. Morris
Transplant Unit, Nuffield Department of Surgery, Churchill Hospital, Headington, Oxford.

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%). 85% 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 UTIs compared with 52% using Cy. 23% compared with 17% had herpetic lesions, and 26% 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.
CYCLOSPORIN USE IN “HIGH RISK” CADAVERIC RENAL TRANSPLANT RECIPIENTS: IS LATE CONVERSION TO AZATHIOPRINE AND PREDNISOLONE SAFE?


The Renal Transplant Unit, Department 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 patients 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.

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

C.J. Taylor, J.R. Chapman, A. Ting, P.J. Morris

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

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 PA26, a monoclonal antibody recognizing an HLA-ABC monomorphic determinant. The results of the donor crossmatches after these treatments are shown in the Table.

<table>
<thead>
<tr>
<th>Crossmatch results</th>
<th>Inferred class and specificity</th>
<th>No.</th>
<th>Grfts functioning at 3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTT digested</td>
<td>Not blocked</td>
<td>17</td>
<td>15 (88%)</td>
</tr>
<tr>
<td>DTT digested</td>
<td>Blocked</td>
<td>7</td>
<td>6 (86%)</td>
</tr>
<tr>
<td>Not DTT digested</td>
<td>Blocked</td>
<td>6</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

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 PA26 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 grafts functioned. This preliminary study suggests that IgG HLA-ABC antibodies are harmful whereas IgM antibodies are not.