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British Transplantation Society

The Royal Free Hospital, Pond Street, London NW3.

10th November, 1982
ANTIBODY THERAPY FOR CYTOMEGALOVIRUS INFECTION AFTER
RENAL TRANSPLANTATION

A.J. Nicholls, C.B. Brown, H. Pox, R. Brown, G. Cathcart, P.L. Yao,
S. L. Noble and I. W. J. McDonald.

The current treatment of cytomegalovirus (CMV) infections after renal transplantation is not satisfactory; the illness contributes significantly to graft loss, morbidity and mortality. Six renal transplant recipients with severe cytomegalovirus (CMV) infection have been treated by passive immunization; one patient received high titre anti-CMV antibody plasma and five patients were given fractionated hyperimmune anti-CMV immunoglobulin. The hyperimmune anti-CMV immunoglobulin was prepared by screening healthy blood donors by indirect fluorescent antibody assays or enzyme-linked immunosorbent assays for anti-CMV titres greater than 1:150, and cold ethanol fractionation of the resulting pooled plasma. The resulting hyperimmune anti-CMV immunoglobulin had an anti-CMV titre of 1:120, 000. All patients treated had been pyrexial for at least seven days before treatment, and had typical clinical and laboratory features of CMV disease including leukopenia, lymphocytopenia, lusus infiltrates, abnormal liver enzymes or deteriorating graft function. Two of the six patients treated showed a complete and sustained response within 24 hours of antibody therapy, but the other four patients did not respond. No side effects were observed.

It is concluded that passive immunotherapy is a highly promising treatment for severe CMV infections, and merits further evaluation.

a) This work has not been previously published.
b) Some of this data has been communicated in a preliminary fashion at a workshop on viral infections in transplantation, European Dialysis and Transplant Society, Madrid, September, 1982.

Non-MHC endothelial antigens in experimental cardiac allograft rejection.

L. C. Paul, R. Blankert and L. A. van Es, Renal Division, Department of Medicine, University Hospital Leiden, The Netherlands.

Previous studies have shown that immunizations of MAXX rats with spleen cells from the MHC-identical BN-strain results in the formation of non-MHC endothelial antibodies. Transplantation of BN kidneys into pre-immunized MAXX recipients results in a donor-specific accelerated rejection, whereas grafting into unmodified recipients does not induce the formation of endothelial antibodies and rejection does not occur. In the present experiments the role of the endothelial antigen in cardiac allografting was studied.

Indirect immunofluorescence studies of BN hearts using MAXX anti-BN or (AC1×MAXX) anti-sera obtained by spleen cell immunizations did not show staining of cardiac endothelium. Grafting of BN hearts into unmodified MAXX recipients did not result in rejection, although endothelial antibodies of the IgG class were detected in 6/8 animals 3-5 weeks after grafting; additional immunizations with spleen cells 112 days after grafting also failed to induce functional rejection as did transplantation into pre-immunized recipients.

We conclude that cardiac allograft rejection is not due to endothelial antibodies but are not rejected, whereas kidney grafts do not induce endothelial antibody formation, but do undergo rejection by circulating antibodies. Quantitative differences in expression of endothelial antigens may explain differences in rejection of both organs.

This work has not been published or read at a scientific meeting previously.
Use of monoclonal antibodies in fine needle aspiration cytology


The Transplant Unit, The Nuffield Department of Surgery, The Churchill Hospital, Oxford. OX3 7LD.

Fine needle aspiration biopsy provides a simple and atraumatic method of monitoring the progress of human renal transplants and can be carried out on a daily basis. Cytological examination of aspirates in 50 patients using light microscopy and conventional histological staining has confirmed the findings of Häyry and von Willibrand showing increasing numbers of macrophages in severe rejection. However, the changes in early rejection are more subtle and identification of some cell types is subjective. Characterization of lymphocyte sub-populations on the basis of morphology is clearly not possible. In a further study in a renal transplant recipient monoclonal antibodies have been used with an immunoperoxidase technique to positively identify and quantitate lymphocyte sub-populations within the graft.

An advantage of this method is that a single aspirate provides several cytocentrifuge slide preparations which may be treated with a range of monoclonal antibodies. This enables the relative number of T lymphocytes, T lymphocytes and sub-populations of helper and suppressor/cytotoxic T cells to be assessed. A number of locally produced monoclonals is in addition to the Ortho and Coulter series of antibodies have been evaluated.

Results indicate that rejection is associated with an increase in suppressor/cytotoxic lymphocytes in the interstitial infiltrate. It is hoped that elucidation of the pattern of cellular reaction within the kidney will provide a more rational approach to immunosuppressive therapy.

References:

This paper has not previously been published, read at a scientific meeting or submitted for consideration by another society.

Presentation or Poster

Is the liver less immunogenic than kidney or heart?

C. Miller, G. Hopi, P.J. Morris.


Liver allografts in the orthotopic position in several different species, are often not rejected (1,2,3,4). This apparent poor immunogenicity is strange bearing in mind the large pool of Ia bearing vascular endothelium in the liver and the extensive population of Ia bearing kuffer cells and dendritic cells.

We have further evaluated this phenomenon by transplantation of an auxiliary liver allograft using the left renal vessels of the recipient for the vascular anastomosis and the ureter for bile drainage. The rat combination DA (RT1b) to FVG (RT1u) which is known to accept orthotopic liver grafts was used. 30 days after the DA auxiliary liver graft had been implanted, a DA heart allograft which was placed end-to-side to aorta/cava.

In contrast to findings with orthotopic liver grafts in this strain combination, all auxiliary liver allografts were rejected within 14 days.

The cardiac allografts implanted 30 days after the liver graft were rejected in a second set fashion.

These results suggest that the apparent lack of immunogenicity of orthotopic liver allografts may be related in some way as yet unexplained to the removal of the host liver.

References:
1. R. Calne et al. 1969 Nature 223, 472-476
2. FA Zimmerman et al. 1979 Trans. Proc. 11, 571-577

This work has not been previously published, read at a scientific meeting or submitted for consideration by another society.
FUNCTIONAL STUDIES OF VEILED (PANETH) CELLS FROM APPENDIX LYNCH

Department of Rheumatology, Clinical Research Centre, Harrow.

Veiled or dendritic cells from different lymph node in in dependent areas of lymph nodes and may be precursors of the para cortical dendritic cells. These cells may play a role in presentation of donor antigens to the host during rejection of kidney grafts. We have separated dendritic cells from the different lymph of normal rabbits or rabbits hyperimmunized with human immunoglobulin and studied their properties in vitro. Mixed lymphocyte reactions in rabbits are generally low, and stimulation of peripheral blood lymphocytes by allogeneic veiled cells was also minimal or absent unless both cell populations were from hyperimmunized rabbits.

The effect of veiled cells in modulating the responses of allogeneic lymphocytes to antigen could, therefore, be studied in the absence of allogeneic stimulation. Small numbers of autologous or allogeneic veiled cells were added to lymphocytes in 20 μl hanging droplet cultures. They enhanced the responses to stimulation with low doses of mitogen or antigen, particularly when the cells were cultured for short periods or at low cell densities. Stimulation was associated with the formation of cellular aggregates which were frequently held together by the processes of a single veiled cell.


References:

This paper has not previously been published, read at a scientific meeting or presented for consideration by another society.
Localization of MHC (HLA-ABC and DR) antigens in 36 kidneys. Differences in HLA-DR staining of tubules between kidneys.

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

The precise distribution of the MHC antigens was studied in biopsies from 36 kidneys which were subsequently transplanted. Monoclonal antibodies to monomorphic determinants of HLA-ABC and DR antigens were used in the peroxidase-anti-peroxidase immuno-histological technique. There was no variation in the expression of HLA-ABC antigens, which were present on all cells of the renal parenchyma. HLA-DR antigens were consistently present on glomerular endothelium and mesangium, intertubular capillaries and interstitial dendritic cells. However, there was a striking variation between individual kidneys in the expression of HLA-DR on tubules. Tubular HLA-DR was present in 57 kidneys (60%) and absent in 11 (23%) and possibly weakly present in another 8 kidneys (17%). Where HLA-DR was found on tubules it appeared to be mainly on proximal tubules.

There was no correlation between tubular HLA-DR expression and donor sex, age, blood group and warm and cold ischemia times. However, there was an increase in the frequency of HLA-DR3, 53% in the negative tubular HLA-DR kidneys compared to 15% in the positive kidneys, which, although not statistically significant, does suggest a possible genetic influence on the expression of tubular HLA-DR.

Graft survival at one year was better in recipients of negative tubular HLA-DR kidneys (70%), compared to 56% in recipients of positive kidneys, but this difference was not statistically significant with the numbers studied.

This work has not been previously published, read at a scientific meeting nor submitted for consideration of another society.
The process of renal allograft rejection is the result of host immunological responses to allo-antigens expressed on the graft.

Animal experiments suggest that a specialized antigen-presenting cell bearing Class II antigen plays a pivotal role in the rejection process. Using a combination of immunofluorescence and cytochemical techniques on cryostat sections of normal and rejecting human kidney, we have attempted to characterize the phenotype of HLA-DR cells.

Reagents used include heterologous antisera to HLA-DR antigens and human Factor VIII, monoclonal antibodies against HLA-ABC (F4/13), monocyte macrophage antigens (FMC-17), interdigitating cell antigens (Ia), adenylate triphosphatase (ATPase) and acid phosphatase (ACP) activities.

We have found that normal human kidney contains a population of HLA-DR cells in the interstitium, 40% of which have the phenotype of endostatin, i.e. Factor VIII, FMC-17. The remaining 20% have an interdigitating morphology and are Factor VIII, FMC-17. In contrast, rejecting kidney contains a vast accumulation of DR cells. Analysis of this population reveals that it is comprised of activated T cells (FMC-17), B cells and activated macrophages (FMC-17). A certain amount of HLA-DR antigen appears not cell bound. We hypothesize that the HLA-DR interstitium interdigitating cells of normal human kidney are the targets of the focal inflammatory cell infiltrates which characterize the rejection process.

The effect of HLA-A, -B, -DR, -M and -HT matching, BENEFICIAL AND DETERIMENTAL TRANSPLANTATION ON THE OUTCOME OF 1,023 LONDON TRANSPLANT GROUP CADAVER RECIPIENTS

H. FESTENSTEIN, N. YEATON, R. IEPKAIA AND J. SIMMS
DEPARTMENT OF IMMUNOLOGY, THE LONDON HOSPITAL MEDICAL COLLEGE, LONDON.

(a) The effect of HLA-A, -B and -DR, -M and -HT matching

The outcome of long term follow-up of 1,023 cadaver transplants were analyzed for the effect of (1) HLA-A and HLA-B antigen matching; (2) HLA-DR, -M and -HT matching; (3) pre-transplant transfusions according to whether the recipients were well or poorly matched for HLA-A and -B; and (4) pregnancies according to the HLA-A and -B matching.

The results show a marked benefit for HLA-A and -B matching indicated by a highly significant difference between observed (O) and expected (E) failures for well matched (O/E: 0.75) and poorly matched grafts (O/E: 2.3) (Peto analysis). Ten years' survival figures for (4+8), (3+7), (1+6) matched grafts were 44%, 26% and 16%, respectively (p<0.001). A similar rank order of survival has been observed in DR matched cadaver grafts.

The well matched group (14 patients) has done particularly well (95% at 2 years), the 1 DR match group (10 patients - 60% at 1 year) and the 0 DR match group (77 patients - 56% at 2 years) - 0/2, 1.27, 0.87 and 0.69 respectively. But even if the DR antigens are compatible, the optimal result depends on the associated good or poor HLA-A and -B matching. MT matching showed a very poor outcome for 2 MT incompatibilities (30 patients - 40% at 63), for 1 (110 patients) and 0 (55 patients) MT incompatibilities at 2 years (O/E: 1.52 vs 0.86). NS also showed a difference but not as striking (4/4 for 2 match vs 8/4 for 0 match pairs).

(b) Blood Transfusions

Pre-transplant transfusions benefited only the poorly matched HLA-A and -B recipients after 3 years, the well matched recipients appeared not to benefit from transfusions after this time. This result was amplified in the recipients who had rejected kidneys or made anti-HLA-A and -B antibodies. Only patients receiving a moderate number of transfusions benefited from this regimen. Multiple transfusions, 20+ produced a result equal to that of 0 transfusions or less.

(a) The work described in this summary has not been previously published.
(b) The work contained in this summary has not been read at a scientific meeting.
Enhancement of rat kidney allograft using haptenated alloantigen and anti-hapten antibody

W.H. Barker, J.V. Hutchinson and P.J. Morris
Buffed Dept. of Surgery, John Radcliffe Hospital, Oxford OX3 9DX

Imune complexes formed with donor alloantigen and anti-donor antibody, or with haptenated alloantigens and anti-hapten antibody, are shown to have specific immunosuppressive properties. We have investigated the possibility of using the latter type of complex to enhance kidney allografts in rats.

Recipients of semi-allogenic or fully allogenic rat kidneys were given immune complexes formed with trinitrophenyl (TNP)-conjugated alloantigens (TNP-Ag) and a mouse monoclonal anti-hapten antibody (anti-TNP). The complexes were administered iv at the time of grafting and, in some cases, also on subsequent days. Immune complexes using TNP-modified whole donor spleen lymphocytes (T-C), cellular membrane monocyte (T-M), and papain solubilized (T-S) alloantigens were found to be effective in enhancing graft survival in specific donor-recipient combinations. Indefinite survival was obtained in some recipient groups with semi-allogenic donors and a more modest degree of enhancement was seen with fully allogenic kidneys. The enhancing effect of TNP-Ag + anti-TNP complexes was highly dependent on the ratio of antigen to antibody, and the optimum ratio varied among strain combinations.

The possible clinical applications of this approach to allograft enhancement will be discussed.

References:

The work described in this summary has not been previously published. Part of this work was presented at the 1982 Congress of the International Transplantation Society.

SYNERGISM BETWEEN ANTILYMPHOCYTE AND ANTIMACROPHAGE AGENTS IN SUPPRESSING ISLET ALLOGRAFT REJECTION.

J.R. BASH and P.R. BELL
Department of Surgery, University of Leicester, Clinical Sciences Building
Leicester Royal Infirmary, Leicester

We have previously demonstrated the ability of the antimacrophage agent silica to prolong islet allograft survival in an F1 hybrid to parent strain model (AS×AUG→AS). In a stronger strain combination (Wag→AS) silica was found to be ineffective. The aim of this project was to study the efficacy of silica in combination with antilymphocyte agents in suppressing the rejection of islets in this stronger strain combination. The islets were harvested using a collagenase digestion and ficoll gradient technique and injected intraperitoneally into the streptozotocin-induced diabetic recipient. Group 1 acted as controls; group 2 received 50mg/100g of silica by intraperitoneal injection on day 1; group 3 received 1ml of antilymphocyte serum (ALS) on days -1, 1, and 3; group 4 received Cyclosporin A(CyA), 20mg/kg dissolved in olive oil, by gavage for 7 days; group 5 received silica and CyA; group 6 received silica and ALS; group 7 received CyA and ALS and group 8 received silica, ALS and CyA. The blood sugar persistently raised above 10mmol/l was regarded as evidence of rejection. The results are shown in the table:

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of rats</th>
<th>No. of days before rejection</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>0.05, 0.1, 0.12</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>0.5, 0.1, 0.12, 0.12</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>0.0, 0.1, 0.12</td>
</tr>
<tr>
<td>6</td>
<td>10</td>
<td>14.2, 22, 33, 33, 33</td>
</tr>
<tr>
<td>7</td>
<td>10</td>
<td>28, 29, 30, 30</td>
</tr>
<tr>
<td>8</td>
<td>10</td>
<td>24.2, 30, 30, 30</td>
</tr>
</tbody>
</table>

In conclusion to this model there is synergism between ALS and Cyclosporin A and between these two agents and silica. This study provides more evidence of the importance of macrophages in islet rejection.

a) The work described in this summary has not been previously published.
b) The work contained in this summary has not been read at a Scientific meeting.
Synergistic immunosuppressive action of procarbazine hydrochloride (PCH) and antilymphocyte serum (ALS) in a rat renal allograft model

Niam Al Nabi, I.V. Hutchinson and L. Brest

Dept. of Immunology, St. Mary's Hospital Medical School, London and Nuffield Dept. of Surgery, John Radcliffe Hospital, Oxford.

The median survival time (MST) of BN (RT1n) to Lewis (RT1b) kidney transplants is greatly improved from 11 days to 37 days by treatment of recipients with both PCH (50 mg/kg on days 1, 3 and 5) and ALS (50 ml/kg on days 2, 4 and 6 after grafting). PCH or ALS alone are weak agents in this combination, giving MSTs of 11 and 14 days respectively. Recipients treated with PCH + ALS fail to make specific antibody and blood or spleen cells from these rats are non-specifically deficient in GVH reactivity. Graft survival is not due to graft adaptation or to opsonization of antigen-reactive cells. Suppressor T cells are present which can specifically prolong the survival of allograft in 400 R irradiated syngeneic recipients and, in mixing experiments, can modulate the GVH reactivity of normal syngeneic lymphocytes. Thus it appears that, as in the mouse, PCH + ALS treatment has a powerful immunosuppressive effect leading to a state of graft acceptance mediated, at least in part, by specific suppressor T cells.

Prestacyclin, aspirin and salicylate in rat cardiac allograft rejection.

Platelet accumulation in acute rejection may contribute to graft failure. This study compared prestacyclin (PG12) infusion in rat cardiac allograft rejection with aspirin (DA) (RT1b) hearts in untreated RVG (RT1c) recipients rejected in 7.3 ± 0.86 days. PG12 i.v. infusion in glycine, 250 mg/kg/min., from day 1 prolonged graft survival to 8.71 ± 0.75 days (Wilcoxon P < 0.01 vs glycine controls). PG12 from day 3 prolonged graft survival to 9.45 ± 1.37 days (P < 0.01 vs controls). Aspirin, 200 mg/kg/day s.c. injection from day 1 prolonged graft survival to 11.27 ± 1.63 days and from day 3 to 12.17 ± 1.02 days (P < 0.01 vs controls). Histology showed that beneficial effects were not due to reduced vascular occlusion.

Sodium salicylate, 300 mg/kg/day by s.c. injection from day 1 gave graft survival from 11 days to over 6 months (median 90 days; P < 0.01 vs aspirin and y controls). ADP-induced platelet aggregation was inhibited by 22% ± 2% in the aspirin treated group but was normal in the salicylate treated group. When added to FVG platelets, 30% inhibition of aggregation was caused by 1.1 mmol/1 aspirin or 14.5 mmol/1 sodium salicylate. Prolongation of graft survival by salicylate was unlikely to be mediated by reduced platelet activity.

SHAW, J.P.L. Department of Surgery, Addenbrooke's Hospital, Cambridge.

a) The work described in this summary has not been previously published.

b) A small part of the work contained in this summary (concerning PG12 and aspirin) has been read at the Surgical Research Society, Sheffield, 9th July 1982.
IN VITRO INTERFERON STIMULATION OF NK AND ADCC EFFECTOR CELLS FROM IMMUNOSUPPRESSED PATIENTS.

P.J. CULLOG, C. R. RABSON, J.S. SEGARITY

University Department of Surgery, St. James's University Hospital, Leeds

Natural killer (NK) cell function is impaired in transplant recipients receiving conventional immunosuppression and this may partially explain the susceptibility of such patients to viral infections. Interferon (IFN) is a potent stimulator of NK and ADCC effector cell function and may have a therapeutic role to play in the treatment of certain viral infections. In these studies we have examined the effects of in vitro IFN stimulation on NK and ADCC mediated by the PBL of the following groups: (1) a healthy control group (n = 14); (2) a group of renal allograft recipients receiving conventional immunosuppression (n = 17); and (3) a group of allograft recipients receiving CYCLOSPORIN A as their sole immunosuppression (n = 11).

Cytotoxicity was measured in a short-term chromium release assay using K562 as the NK target and a rabies-antibody-coated lymphoblastoid cell line (LLN13) as the ADCC target. NK and ADCC were measured before and 1 hour after incubation with 1000 U/ml of pure human lymphokinetic interferon. The results were as follows:

<table>
<thead>
<tr>
<th></th>
<th>K562</th>
<th>AB-LLN13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-IF</td>
<td>Post-IF</td>
<td>Pre-IF</td>
</tr>
<tr>
<td>Controls</td>
<td>34.9 ± 7.1%</td>
<td>50.6 ± 6.3%</td>
</tr>
<tr>
<td>As + ?</td>
<td>10.7 ± 9.9%</td>
<td>24.9 ± 19.8%</td>
</tr>
<tr>
<td>CyA</td>
<td>23.1 ± 10.0%</td>
<td>33.6 ± 13.2%</td>
</tr>
</tbody>
</table>

Although NK function is impaired in both conventionally immunosuppressed patients and those receiving CYCLOSPORIN A, this may be partially restored by IFN stimulation. Impaired ADCC after conventional immunosuppression may also be restored but CYCLOSPORIN A does not appear to alter ADCC function.

These data provide some rational basis for the use of IFN in the treatment of certain viral infections in immunosuppressed patients.

a. The work described in this summary has not been previously published.

b. The work contained in this summary has not been read at a scientific meeting.

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CYCLOSPORIN A SERUM LEVELS AS A MONITORING ASSAY - FACT OR FICTION

A. Bell, J.E.M. Albano, C.J. de Sara, J.R. Parry, M. Sipak,
Medicine Regional Transplant Unit, St. Mary's Hospital, Portsmouth, U.K.

Serum estimations of CYCLOSPORIN A (CyA) by radioimmunoassay may be a useful guide to effective immunosuppression (I-S) on one hand and the avoidance of nephrotoxicity on the other. A comparison was made between samples obtained with known values from the Homerton Hospital. This showed a mean difference in the estimations of 3.1 ± 3.0 ng/ml. 26 patients had CyA assay performed at frequent intervals 1-5 weeks after cadaveric renal transplantation (CRT). Oral, intramuscular and intravenous CyA was given according to our recently published protocol.

RESULTS. CyA levels of 6 patients with rejection episodes before day 25 and 6 patients with rejection episodes latest than 25 days after CRT showed no statistical difference at any time compared to 12 patients without rejection although there was a trend towards an increased mean CyA level in the first week in patients without rejection (Table 1).

<table>
<thead>
<tr>
<th>Week 1</th>
<th>Early Mean Serum CyA Level ± SD (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reactor</td>
<td>Late Non</td>
</tr>
<tr>
<td>Reactor</td>
<td>256.6 ± 260.6</td>
</tr>
</tbody>
</table>

CyA levels of 13 patients in whom CyA nephrotoxicity was proven by either biopsy or the therapeutic effect of dose rejection were compared with 13 patients who showed no evidence of nephrotoxicity. There was no significant difference between the mean CyA levels at any time after CRT. There was marked variation in the serum level of those patients receiving identical oral dose of CyA. Of 13 courses of methyl prednisolone pulse therapy 21 showed a mean increase in CyA level of 219%. Our experience with CyA serum levels at present does not allow interpretation of any given level as being definitely nephrotoxic or as correlating with an I-S efficacy. Levels may be helpful as one factor of many in reaching a decision about these two crucial parameters in renal transplantation.

2. Lancet CB (8289), 57-60 (July 1989).

This paper has not been previously published or read at a scientific meeting or submitted for consideration by another society.
Early experience of cyclosporin A in clinical heart transplantation

Wallwork, J
Conyngham, R
English, T A H

Department of Cardiovascular Surgery, Papworth Hospital, Papworth Everard, Cambridge.

Since March 1982 Cyclosporin A has been incorporated into the immunosuppressive regimen of 11 (10 male and 1 female) consecutive cardiac recipients. Follow up is from 1 month to 7 months with 9 current survivors.

Previous experience with Cyclosporin A and other additional immunosuppressive agents in cardiac transplantation suggested that patients were over-immunosuppressed.

As a result our initial protocol was Cyclosporin A (18 mg/kg per day initial dose), in conjunction with low dose prednisolone (0.3 mg/kg per day). Two severe and two moderate rejection episodes occurred in 6 patients on this regime, with one death at 8 days post-transplantation. As a result additional antithymocyte globulin (ATG) to maintain T cells at 1x for 10 days was incorporated into the immunosuppressive regime for subsequent patients.

There have been 2 mild rejection episodes prior to discharge in 5 patients on this regime. Rejection episodes have been treated with methylprednisolone + equine ATG, or augmentation of Prednisolone.

Five infective episodes have occurred in 4 patients (2 bacterial, 1 CMV + fungal, 1 toxoplasma) in the early post-operative period (0-3 months) with no death from disseminated toxoplasmosis. An additional late infection at 6 months (pneumocystis) has occurred.

Cyclosporin A nephrotoxicity of mild or moderate nature has occurred in all patients, responding to reduction in Cyclosporin A dose and serum levels. 80% of patients have left hospital with a mean stay of 33% less than 29 previous transplant patients. Refinements of Cyclosporin A immunosuppressive therapy will be made as a result of continued evaluation.

Synergism between salicylate and cyclosporin A in rat cardiac allotransplants

Although cyclosporin A (CyA) is a powerful immunosuppressant, the dose-related nephrotoxicity in humans can present clinical problems. Perhaps a combination of CyA with other non-steroidal drugs would allow a non-nephrotoxic dose of CyA to be used, yet still avoiding steroidal side-effects. DA (RT1a) hearts were transplanted heterotopically to PVG (RT1b) rats and cessation of graft beat taken as the end-point of rejection. Treatment was given by daily subcutaneous injection for 30 days unless grafts rejected earlier than this.

Results:

<table>
<thead>
<tr>
<th>Drug Therapy</th>
<th>Number of Rats</th>
<th>Mortality</th>
<th>Mean CyA Level (mg/ml)</th>
<th>Graft Survival (days)</th>
<th>Median</th>
<th>Milgrom Compares with Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline 0.6 ml</td>
<td>10</td>
<td>0</td>
<td>&lt;20</td>
<td>7(x1), 0(x2)</td>
<td>7.4</td>
<td></td>
</tr>
<tr>
<td>CyA 2 mg/kg in olive oil</td>
<td>7</td>
<td>0</td>
<td>133 ± 128</td>
<td>7(x1), 8(x2), 10(x1)</td>
<td>7.9</td>
<td>N.S.</td>
</tr>
<tr>
<td>Sodium Salicylate 100 mg/kg in saline</td>
<td>8</td>
<td>0</td>
<td>&lt;20</td>
<td>7, 11, 17, 19(x4)</td>
<td>6.6</td>
<td>N.F.</td>
</tr>
<tr>
<td>CyA 2 mg/kg + Sodium Salicylate 100 mg/kg</td>
<td>11</td>
<td>0</td>
<td>131 ± 89</td>
<td>9(1), 50(x20)</td>
<td>&gt;60</td>
<td>P&lt;0.01</td>
</tr>
</tbody>
</table>

There was a definite synergistic effect between sodium salicylate and CyA in the prolongation of heart allotransplant survival. Similar results are being obtained in other rat strain combinations.

Shaw, J.P.L. Department of Surgery, Addenbrooke's Hospital, Cambridge.

a) The work described in this summary has not been previously published.
b) The work contained in this summary has not been read at a scientific meeting.