History ✓
Progs ✓
USA

Tonne – 15 min back

Pay. Allow committee to get their lunch

David White to chair last session.

Buffet places

List of sponsors : Glaxo
Gambro
Hoescht
Upjohn

Medical School
RFH / [illegible] / Elg. Drack, Mr. ~~[illegible]~~ (projector)

Details of [illegible] + requests for abstracts will be sent soon. → BSM

Future meetings
History
Univ. Surgeons ERF's
Circulate of SRS leaders
when to hold AGM

Recommendation to use of life table analysis (reference will be given)

Presentation of papers ([illegible])

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BRITISH TRANSPLANTATION SOCIETY

1979 Spring Meeting

ROYAL FREE HOSPITAL

Wednesday 4th April, 1979

TIMETABLE

Local Organiser : O. Fernando

10.00 a.m.	Coffee
10.30	PAPERS 1 — 10 (Clinical Transplantation) Chairman : Mary McGeown
1.00 p.m.	Sandwich Lunch
2.00	Business Meeting
2.45	PAPERS 11 — 14 (Experimental Transplantation) Chairman : P. McMaster
3.45	Tea
4.00	PAPERS 15 — 18 (Histocompatability Antigens) Chairman : Valerie Joysey
5.00	Society Reception and Buffet

1. THE IN VITRO RESPONSE TO CONCANAVALIN—A OF PERIPHERAL BLOOD MONOUCLEAR CELLS FROM PATIENTS UNDERGOING CHRONIC HAEMODIALYSIS

P. J. Guillou, Linda Woodhouse, G.R. Giles.

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

Lymphocyte transformation in response to the T-cell mitogen Concanavalin-A (Con-A) in vitro is considerably increased by a preliminary 24-hour incubation period prior to the addition of Con-A. This phenomen may be quantified and used as an indirect parameter of human suppressor cell activity (Feighery et al, 1978). Since it is known that uraemic patients are anergic and exhibit impaired in vitro lymphocyte responses to other T-cell mitogens such as PHA, it is of interest to establish whether or not suppressor cell function is also impaired in such patients as this may be of importance in allograft survival.

Eighteen control subjects and 18 chronic haemodialysis patients (CHD) have been studied. The total T-cell population of the CHD group (0.93 $\pm$) was significantly ^{3} 0.48 x 10 ^{3} /mm lower than that of the control group (1.46 $\pm$ 0.62 x 10 ^{3} /mm ^{3}< d) (0.01). In addition when Con-A was added from the initiation of culture the mean blastogenic response per 10 ^{5} T-cells of the control group (14,997 $\pm$ 8,c.p.m.) was significantly higher than that of the CHD group (9,264 $\pm$ 4,927 c.p.m.) ($p < 0.05$, $t = 2.43$). This difference disappeared when the addition of Con-A to the cultures was defered for 24 hours (controls 26,639 $\pm$ 16,367 c.p.m. v CHD group 21,509 $\pm$ 12,053 c.p.m.). However the mean percentage reduction in Thymidine incorporation which Con-A was added at time 0 compared with when it was added at 0 + 24 hours was greater in the CHD group (mean $\pm$ S.D. = 56.8% $\pm$ 12.4%) than in the control group (mean $\pm$ S.D. = 45.0% $\pm$ 14.8%) ($t = 2.59$, $p < 0.02$).

These results suggest that the relative anergy of chronic haemodialysis patients may be attributable to both impaired lymphocyte responsiveness and a general reduction in the total T-Cell population. However suppressor cells appear, in part at least, to be spared this lymphocyte depletion.

Feighery, C. A., Whelan, C. A., Weir, D. G. and Greally, J. F. (1978) Clin. Exp. Immunol. 32: 459

2. RELATIONSHIP BETWEEN DNCB SKIN TESTING, LYMPHOCYTE RESPONSE TO MITOGENS AND OUTCOME OF RENAL TRANSPLANTATION

D.N.H. Hamilton, V. Jackson, J. D. Briggs

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

Pre-transplant skin testing with dinitrochlorobenzene (DNCB) has shown that those regular dialysis treatment patients (RDT) with residual endogenous cell-mediated immunity reject their kidney allografts earlier than those with a low or absent response to DNCB (Rolley et al., 1977: Diamondopoulos et al., 1978). In the present study the response of lympocytes from normal and RDT patients to the mitogens PHA, Con A and PWM were compared. Further comparison was then made between the responses in RDT patients according to DNCB testing.

1) RESPONSE OF LYMPHOCYTES (STIMULATION INDEX IN CONTROL PLASMA) FROM NORMAL AND RDT PATIENTS TO MITOGENS

	PHA	PWM	ConA
Control	114 $\pm$ 19	48 $\pm$ 11	24 $\pm$ 6
RDT	89 $\pm$ 21	38 $\pm$ 8	10 $\pm$ 2
	n.s.	n.s.	$P < 0.05$

2) COMPARISON OF LOW AND HIGH DNCB RESPONDERS TO MITOGENS

DNCB Score	PHA	PWM	ConA
0 — 3	50 $\pm$ 11	33 $\pm$ 6	5 $\pm$ 2
3 +	139 $\pm$ 45	62 $\pm$ 13	16 $\pm$ 2
	$P < 0.01$	$P < 0.01$	$P < 0.05$

These results show a modest depression of the response to mitogens in RDT patients when compared to normal but a marked depression of stimulation in low DNCB responders when compared to high DNCB responders.

These results suggest that one defect in the failure to respond to DNCB is a depressed lymphocyte reactivity.

Rolley, R., Sterioff, S., Parks, L. and Williams, G. (1977)
Tranplantation Proceedings 9, 81.
Diamondopoulos, A. A., Hamilton, D. N. H., Briggs, J. D. (1978)
Dialysis, Transplantation and Nephrology 15, 283.

3. EFFECTS OF TEMPERATURE AND METHOD OF STORAGE ON HEPATIC FUNCTION

B.J. Fuller and V.D. Attenburrow

Academic Department of Surgery, Royal Free Hospital.

A problem in liver transplantation is the inability to store livers for a clinically-useful time prior to transplantation. It became apparent from our transplantation studies in the pig that it was very difficult to assess the effects of preservation on early liver function because of the complicating factors of anaesthesia, drug administration and transfusion necessitated by the operation. We have used an isolted rat liver model to investigate hepatic function after storage and the present studies were undertaken to study the effects of storage temperature, since a recent report has shown that higher temperature improved kidney preservation by continuous perfusion (2).

The technique of liver isolation and storage has been described previously (3). Four groups of experiments were carried out. In Group A livers were stored for 24 hr at 6° C by simple hypothermia after flushing, whilst in Group B continuous portal perfusion was carried out. Group C livers were preserved at 10° C by simple hypothermia, and in Group D the livers were continuosly perfused, also at 10° C. At the end of the 24 hr preservation period samples of tissue were taken to estimate tissue water gain, K + loss as indicated by the K + /Na + ratio, and active metabolism in prepared tissue slices by measuring urea synthesis and galactose uptake. The results can be seen in the following table, in which values for control livers are also presented.

	Tissue Water Content (g H_2O/g dry wt)	Tissue K+/Na+ ratio	Urea Synthesis umol/g	Galactose Uptake umol/g
Controls (16	2.38 ± 0.11	3.00 ± 0.32	9.14 ± 0.81	44.68 ± 6.32
Group A (6)	3.87 ± 0.09	0.32 ± 0.10	1.63 ± 0.47	30.16 ± 3.27
Group B (6)	3.45 ± 0.09	0.54 ± 0.06	4.93 ± 0.90	29.78 ± 8.33
Group C (6)	3.21 ± 0.22	0.49 ± 0.04	0.58 ± 0.16	22.13 ± 4.28
Group D (6)	2.41 ± 0.10	0.86 ± 0.06	8.28 ± 1.20	38.12 ± 6.13

From these results it would appear that by far the most successful method of storage is continuous perfuson at 10 °C. The two groups of livers stored by flushng alone showed poor function on all counts, and partcularly so at 10° C. Perfusion at 6 °C was accompanied by a reduced metabolic activity and significant tissue oedema. In the clinical situation perfusion is costly and requires skilled supervision, but our present results show that further investigations into flush storage are required to minimise the harmful effects if this is to be the method of choice. This is particularly so since our own experience of flush cooling large livers, as in the pig, has shown that it requires large volumes of ice-cold perfusate to reach and maintain core temperatures below 10 °C during harvesting and storage.

1. Pegg, D. E., Jacobson, I. A., Walter, C. A. (1977) Transplantation 24, 39,
2. Fuller, B. J., Attenburrow, V. D., Newsome, C. (1978) Cryobiology 15, 279.

4. THE INFLUENCE OF ISCHAEMIA ON THE BILIARY TRACT

P. McMaster, R.M. Walton, D.G.D. Waight, R.K. Medd, T.P. Syrakos

Departments of Surgery and Pathology, University of Cambridge.

Excellent hepatocyte function has been recorded following hepatic storage, but little attention has been directed to the influence of such ischaemic time on the biliary tract and damage to the biliary tract may occur prior to transplantation which may result in biliary complications after liver transplantation.

PART 1 Histological studies of the biliary tract were undertaken at the end of hepatic storage to assess the intergrity of the biliary tract in the last ten human liver transplants. Total ischaemic time 5.4 hours ± 3.1 S.D. and in seven patients severe biliary tract damage was seen in spite of excellent hepatocyte function. This was subsequently associated with biliary tract complications.

PART 2 The pig is an animal which has been widely used in both transplantation and hepatic ischaemic studies and this animal was used to evaluate the impact of extended warm ischaemia and prolonged cold storage. A model of hepatic and biliary tract warm ischaemic damage was developed which allowed animal survival with a shunt allowing simultaneous splanchnic decompression with intubation of the inferior vena cava and thus total isolation of the liver.

In eight animals this technique was established although, because of technical difficulties in situ, only six animals survived. Transient rises in bilirubin and liver transaminas levels were recorded and animals were re-explored on the fifth day and the gall bladder removed and histological studies carried out on the liver and biliary tract. All animals then survived a further 3 weeks. This period of warm ischaemia, considerably in excess of the normally accepted maximum warm ischaemic period of the liver produced no evidence histologically or electron microscopically of biliary tract damage.

However, in a second model, in which the liver was removed and subjected to standard intraportal perfusion with Hartmann's and plasma protein fraction and then storage at 4° C for up to 24 hours, extensive histological damage both to the biliary tract and the intrahepatic biliary canaliculi was seen. In spite of this excellent preservation of hepatocyte was maintained.

This failure of standard hepatic harvesting to preserve the integrity of the biliary tract has led to a further evaluation of the clinical programme which now incorporates a biliary perfusion technique using plasma protein fraction to perfuse the biliary tract with initially very encouraging results.

5. DOPAMINE PRE-TREATMENT IN THE UNSTABLE KIDNEY DONOR

A.T. Raftery and R.W.G. Johnson

University Department of Surgery, Manchester Royal Infirmary.

The unstable kidney donor is defined as patient where, despite intravenous fluids and diuretics there is persistent hypotension associated with oliguria or anuria. Carroll et al (1969) have shown that avoidance of a prolonged period of hypotension improves the quality of cadaveric kidneys.

Fifteen unstable donors have been treated with dopamine (Intropin) starting with an initial dose rate of 2 ug/Kg/min and titrating the dose against the response in blood pressure and urine output. The response is shown in the Table.

Pressure of hypotension Mean (range)	286 min	(30 — 780)
Systolc blood pressure before dopamine Lowest recorded. Mean (range)	55 mm Hg	(30 — 100)
Systolic blood pressue after dopamine Average recorded. Mean (range)	135 mm Hg	(100 — 220)
Urine output before dopamine Lowest recorded. Mean (range)	6 ml/mr	(0 — 15)
Urine output after dopamine Average recorded. Mean (range)	175 ml/hr	(50 — 500)

Prior to donor nephrectomy the following premedication was given intravenously, methylprednisolone 1G, Frusemide 120 mg, chlorpromazine 50 mg, phenoxybenzamine 100 mg, phentolamine 5 mg and heparin 10,000 units. Donor nephrectomy was performed after cardiac arrest and the kidneys were perfused with modified plasma protein fraction on a Gambro perfusion apparatus until transplantation. Thirty kidneys from these patients were transplanted. Seventeen functioned immediately attaining a mean creatinine clearence of 63 ml/min (range 10 — 115). Ten showed delayed function eventually attaining a mean creatinine clearance of 34 ml/min (range 15 — 46). Three never functioned.

It is suggested that a dopamine infusion will improve renal function in the unstable donor and increase the chance of viable organs for transplantation.

Carroll, R. N. P., Chisholm, G. D. and Shackman, R. (1969) Lancet, 2, 551.

6. RENAL TRANSPLANTATION WITH MULTIPLE ARTERIES

M. Fox and R. Yalin

Hallamshire Hospital, Sheffield.

Multiple arteries present problems to the transplant surgeon, increasing technical skills needed and prolonging ischaemic times. Past reports have shown an increased incidence of post-operative complicatons and poorer final prognosis compared with that of kidneys supplied by single arteries [1] — [3]. Our experiences have been considerably more favourable than that of previously published series.

Out of a total of 184 transplant operations performed in the Sheffield Renal Transplant Unit there were 27 kidneys with two or more renal arteries requiring separate anastomosis. The anastomoses were performed either to the two major branches of the internal iliac artery or separately to the internal and external arteries end-to-end or end-to-side. Interrupted sutures were used in all cases. Techniques and management are described particularly in relation to small polar vessels. Ischaemic times were incresed compared with those of kidneys with single arteries, but incidence and duration of acute tubular necrosis and also the length of time spent hospital was similar in both groups. Excessive bleedng was no more common than following single arterial anastomosis and there were no cases of post-operative haemorrhage, infection, renal artery stenosis or mortality. Incidence of post-operative urinary fistula was increased, but with satisfactory final outcome.

1. Spanos, P. K., Simmons, R. L., Kjellstrand, C. M. et al. (1973) Am. J. Surg. 125, 554.
2. Goldman, M. H., Tilney, N. L., Vineyard, G. C. et al. (1975) Surg. Gynaec. and Obstet. 141, 758.
3. Hall, C. L., Sansom, J. R., Obeid, M. et al. Brit. Med. J. 2, 667.

7. SOME PROBLEMS IN THE ASSESSMENT OF RENAL TRANSPLANTS

E. P. Wraight, S. Thiru, A. Dennisod, R. Y. Calne

Addenbrooke's Hospital, Cambridge.

^{99}mTc DTPA studies are valuable in assessing renal transplants but the diagnosis of rejection is often difficult unless serial studies are carried out at frequent intervals. In some cases, examples of which will be presented, the findings can mimic those in acute tubular necrosis (A.T.N.) Renal accumulation of ^{99m} Tc S-colloid has been proposed as a specific indication of rejection*. We have carried out 98 such studies in 58 patients clinically suspected of rejection. A definite diagnosis could be established at the time of 63 studies (45 histologically). The true positive rate was 68% (27/40) and the false positive rate 17% (4/23). Interpreted with caution, S-colloid uptake can be helpful in the management of renal transplant patients.

In 9 out of 11 patients being treated with Cyclosporin A to suppress rejection, the results of dynamic imaging with ^{99m}Tc DTPA were identical to those seen in A.T.N. Those findings suggest that this drug can be nephrotoxic, particularly affecting the tubules, and this has been confirmed histologically in some cases. ^{99m} Tc DTPA studies will have to be interpreted with caution if Cyclosporin finds a place in the routine management of renal transplants.

*George, E. et al. (1975) Radiology 116, 121.

8. LOW DOSE STEROID FROM THE DAY FOLLOWING RENAL TRANSPLANTATION

Mary McGeown, J. F. Douglas, W. A. Brown, R. A. Donaldson, J. A. Kennody, W. G. Loughridge S. Mehta, Claire Hill.

Renal Unit, Belfast City Hospital.

High dosage of steroid may lead to obesity, cushingoid appearance, increased risk of death from infection, gastrointestinal complications, diabetes or serious disability from avascular necrosis of bone. Despite these disadvantages many units use larges doses of steroid after renal transplantation.

We have used a low dose of steroid (20 mg of prednisolone) commencing the day after transplantation, for 151 consecutive renal transplants (146 cadaver, 5 living related donors). The only other immunosuppressive drug used is azathioprine.

109 out of 151 grafts continue to function for periods of one month to 10 years and of 42 grafts lost 17 failed rom rejection; furthermore 11 grafts were functioning well at the time of death of the patient for reasons unconnected with transplant or immunosuppression. The comparitively small number of grafts lost from rejection shows that low dosage of steroid combined with azathioprine provides effective immunosuppression.

No patient has died from infection during the first three months after transplantation and the overall infection rate has been low. One patient only has died from gastrointestinal disease. Two patients developed acute hyperglycaemia; both survived. No patient has required hip joint replacement and only two have hip pain (in one, hip joint disease antedated the transplant). All patients are currently being screened for asymptomatic avascular necrosis; so far no further cases of avascular necrosis have been discovered.

The low incidence of graft failure due to rejection as well as the low incidence of serious complications suggest that low dose of steroid is satisfactory treatment for immunosuppression for renal transplantation.

9. PRELIMINARY STUDIES ON CYCLOSPORIN A USING THE RAT KIDNEY ALLOGRAFT MODEL

W. P. Homan, J. W. Fabre, P. R. Millard, P. J. Morris

Nuffield Departments of Surgery, Radcliffe Infirmary, Oxford.

The enthusiasm which first greeted cyclosporin A has been tempered by the growing number of unsolved problems associated with its use. Included among these problems are the optimal dosage, the route of administration, cyclosporin's absorption or lack of absorption from the gastrointestinal tract, its mechanism of action, and its possible nephroxicity.

To gain insight into some of these largely unanswered questions, cyclosporin was studied using the difficult DA to Lewis rat kidney allograft model. Delaying the removal of the rats' own kidneys until day 7 allowed histologic examination for toxic effects of the drug without the complicating factor of rejection. Concurrent biopsy of the transplanted kidney provided information on the modification of the immune response with varying doses of cyclosporin. In addition, a safe technique for intravenous administration of cyclosporin was devised to obviate the problem of parenteral administration, where this is necessary.

Results from this study indicate that cyclosporin: (1) is very effective in prolonging graft survival in low doses in the rat kidney allograft model; (2) is well absorbed from gastrointestinal tract when given orally in olive oil; (3) is approximately twice as effective when given intravenously as when given orally; (4) seems histologically to abrogate the antibody mediated damage of acute rejection while not affecting the mono-nuclear cell responses; (5) by itself causes no histologically identifiable changes in the kidney; and (6) is apparently free from untoward effects, specifically infection, in the model studied.

10. SUCCESSFUL RENAL TRANSPLANTATION IN A PATIENT WITH COMPLETE ABO AND HLA INCOMPATIBILITY BY THE USE OF PLASMAPHERESIS

M. Slapak, R.B. Naik, H.A. Lee

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

There is uniformity of opinion that a major breach of ABO compatibility between donor and recipient leads to early and rapid graft desruction.

This communication describes a patient's clinical course after inadvertantly receiving a cadaver graft from a donor (Group A) to which he (Group O) was incompatible. In addition all four HLA specifications were miss matched. Initially renal function was good. Within 2 days of transplantation however, the patient developed a clinical condition characterised by malaise, oliguria, haematuria and graft tenderness. There was a rise in serum creatinine and a marked fall in anti A antibody. A biopsy on day 5 showed the classical appearances of intra-renal, intra-vascular coagulation. A six day course of plasmapheresis was instituted, each time 3 litres of plasma being withdrawn and the anti A antibody being specifically removed by absorption before returning the plasma to the patient. Within 12 hours of the first exchange, clear cut clinical, biochemical and immunological evidence of benefit was seen. Near normal renal function was present by the fourth exchange.

Further histologically proven rejection episodes in which histological features of intra-vascular were absent were later successfully reversed by 2 further courses of plasmapheresis. He remains entirely well after 8 months post transplantation. The patients clinical course demonstrates the specificity of plasmapheresis in reversing the clinical and histologically proven manifestations of intra-renal, intra-vascular coagulation and questions an accepted dogma.

11. THE EFFECTS OF ISCHAEMIA ON RENAL TISSUE GROWTH AFTER CONTRALATERAL NEPHRECTOMY

I. Paptheofanis, R. A Sells

Royal Liverpool Hospital.

It is well known that renal hyperplasia and hypertrophy follows unilateral nephrectomy in the rat kidney. We have investigated the added effects of ischaemia and immunosuppression on renal growth in the rat after unlateral nephrectomy.

METHOD: Left nephrectomy was performed under sodium pentobarbitone anaesthesia in 100 G wistar male rats. When necessary right renal ischaemia was induced by clamping the right renal pedicle, for 50 minutes. 50 ^{125}—Iodo—2—deocxuridine, which is a DNA percursor, was used to estimate the hyperplastic response. This was injected I.P. 16 hours before the animals were killed at various intervals post-nephrectomy. The right kidney was then excised, weighed and counted. The dry weight was measured following incubation at 93° C for 15 hours. Groups of animals were studied, with controls, 2 days and 7 days after left nephrectomy.

RESULTS: (Mean values ± S.D.)

	DAY 0		DAY 2		DAY 7	
	cpm/mg	Dry. Wt (G)	cpm/mg.	Dry. Wt. (G)	cpm/mg	Dry. Wt. (G)
1. Control Non-Nephrectomized	8.1 ± 1.2	.0953 ± .0088	8 ± 1.2	.1085	8 ± 1.2	.1367 ± .0051
			**			**
2. Left Nephrectomy only	—	—	21.8 ± 3.2	.1476 ± .0087	12.26 ± 2.47	.1935 ± .0153
			**			
3. Left Nephrectomy ± R controlled Ischaemia	—	—	40.6 ± 4.9	.1441 ± .0121	16.3 ± 4.97	.2092 ± .0162

**p > 0.001.

COMMENT: Ischaemia is followed by an increase in hyperplasia at day 2 and day 7 compared with controls and non-ischaemic single kidneys. Preliminary studies on the addition of immunosuppressive drugs to the above regime will be presented, which suggests that the regeneration processes following ischaemia are impaired by Azathioprine but not by Methyl-prednisolone.

12. TRANSPLANTATION OF THE DUCT-LIGATED PANCREAS IN THE DIABETIC RAT AND EFFECTS OF HYPOTHERMIC PRESERVATION

Pauline F. Boyle, B. Fairbrother, R. Yalin, D.N. Slater and M. Fox

Transplant Unit, Royal Hospital, Sheffield.

Transplantation of isolated islets of Langerhans, although successful in the treatment of diabetes in the experimental animal, has not been found to be applicable to the human. It is for this reason that we have re-examined the possibility of grafting of the pancreas on a vascular pedicle, but without duct drainage in view of isolated experimental and clinical successes (Reemtsma et al., 1963, Kryiakides et al 1976, Svahn et al 1978).

Inbred Agus rats were used as experimental animals and a microsurgical technique was developed to transplant the pancreas into rats previously made diabetic with Streptozotocin. The pancreas was transplanted on a segement of aorta end-to-side to the host aorta in the abdomen and the donor portal vein was anastomosed end-to-side to the inferior vena cava at about the same level. Colins' solution at 0 — 4 °C was used for arterial flushing prior to anastomosis, and the organ was left in the same solution for the preservation studies.

Following successful grafting, normoglycaemia was acheived within 24 hours and glucose tolerance curves were normal one month later. When the transplanted pancreas was subsequently removed, return to the diabetic state occurred. Histology of the pancreas was studied following transplantation. Appearances of islet tissue remained normal but a moderate amount of interstitial fibrosis and marked atrophy of exocrine tissue were seen. The effect on the pancreas of cold ischaemia of 1 to 24 hours' duration was examined. Results obtained so far have shown that the maximum time of cold ischaemia tolerated for return to normo-glycaemia was 15 hours.

Kyriakides, G. K., Vijender, K. A., Lifton, J. et al. (1976) J. Surg. Res. 20: 541.
Reemtsma, K., Lucas, Jr. J. F., Rogers, R. E., et al (1963) Annals Surgery 158: 645.
Svahn, T., Lewander, R., Hardstedt, et al (1978) Acta Radiologica Diagnosis 19: Fasc. 2, 297.

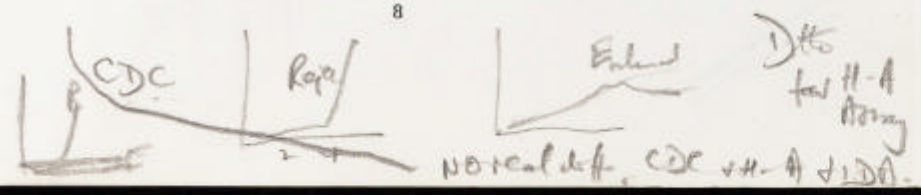
13. ANTIBODY RESPONSES TO DONOR ANTIGENS DURING ENHANCEMENT OF RAT RENAL ALLOGRAFTS

G.R.D. Catto, M. Suthanthiran, A. Kaldany, K. George, M.R. Garovoy, T.B. Stroma and C.B. Carpenter

Departments of Medicine, Harvard Medical School and University of Aberdeen.

Rat renal allografts are enhanced by the administration of hyperimmune recipient anti-donor serum (Soulillou et al., 1976). Kinetics of humoral immunity were studied in 10 Lewis (Lew) recipients of Lew x Brown Norway (LBN)F$_1$ kidney grafts. Enhancement was produced by passive transfer of Lew anti-BN serum. Sera obtained from 6 rejecting and 4 enhanced animals on days 0, 2, 4 and 7 post transplantation were assayed for complement-dependent cytotoxicity (CDC), haemagglutinating antibodies (HA) and lymphocyte dependent antibody (LDA). EA rosette inhibition assay (EAI) was used to detect anti-Ia antibodies. CDC, HA and LDA did not differentiate clearly between rejecting and enhanced animals. In contrast, EAI was detected in 6/6 rejecting and 0/4 enhanced animals. Furthermore, the acid eluate obtained from rejecting kidneys caused both EAI and HA whereas that from enhanced kidneys produced both detectable EAI. Thus antibody responses to Ag-B and Ia antigens differ in rejection and enhancement.

Soulillou, J. P., et al., (1976) Journal of Experimental Medicine: 143, 405.



14. IMMUNOLOGICAL CHARACTERISATION OF NORMAL HAEMOPOITIC PRECURSOR CELLS AND ITS RELEVANCE FOR BONE MARROW TRANSPLANTATION

G. Jannossy, D. Crawford, K. Bradstock, H.G. Prentice, and C. Hetherington

Department of Immunology and Haematology, Royal Free Hospital and Clinical Research Centre, Harrow.

In the last few years well characterised antisera have been prepared against leukaemia associated antigens (e.g. ALL antigen, Ia-like antigens, terminal transferase enzyme). These reagents are used in leukaemia diagnosis. They can also be applied in various combinations labelled with different fluorochromes as single cell assays in order to characterise rare bone marrow cells. These cells are putative haemopietic and lymphoid precursors. These combined single cell assays can be used to analyse the exact reactivity of monoclonal antibodies (made by mouse B cell-meloma hybrids) against rare human bone percursors. This is important because well characterised antisera produced in large quantities could open up new possibilities for immunological manipulations during autologous bone marrow transplantation (i.e. removel of residual leukaemic cells) or during allogeneic transplantation (i.e. removal of T lymphoid cells). Furthermore, preliminary experiments suggest that some reagents (e.g. anti human Ia-like antisera) cross-react with marmoset bone marrow precursors and B cells, and can be tested during bone marrow transplantation between chimeric marmosets. This system provides a model for human autologous bone marrow transplantation.

15. REQUIREMENT OF LD-IMMUNOGENS IN ACTIVE ENHANCEMENT OF RAT CARDIAC ALLOGRAFTS

W. Lauchart, B.J. Alkins, and D.A.L. Davies

Wellcome Lab. of Exp. Pathology, St. Marys Hospital Medical School and G. D. Searle Research Lab.

The rejection of heterotopic auxiliary heart allografts in rats can be abrogated by administration of antisera against donor LD-determinants after transplantation (passive enhancement (1). The present experiments tested the use of donor cells as immunogens for active enhancement in a cardiac allograft system (Lewis x Brown Norway)F$_1$ into Lewis). Various populations of 10^7 BN donor cells either purified erythrocytes (RBC), peripheral blood lymphocytes (PBL), spleen cells, nylon wool adherent (B-Lymphocytes) or nylon wool non-adherent (T-Lymphocytes) spleen cells were given i.v. 7 days prior to grafting. The results are summarized below:

Treatment	Transplant Survival (days) MST	SD	n	p*
None (Controls	7.7	± 0.7	5	
RBC	8.4	± 2.5	7	n.s.
T-Lymphocytes	9.0	± 2.6	6	n.s.
PBL	12.8	± 3.3	5	0.0025
Spleen Cells	15.6	± 3.8	5	0.001
B-Lymphocytes	16.5	± 2.2	6	0.0001

*Student-t-Test, versus control group

RBC and T-lymphocytes, which carry no LD-antigens on their surface, did not prolong graft survival. Administration of PBL, Spleen Cells or B-enriched lymphocytes led to a significant prolongation of graft survival. This suggests that donor B-cells produce active enhancement possibly by inducing anti-Ia-antibodies.

1. Davies, D. A. L., Alkins, B. J.: (1974) Nature 247, 294.

16. RENAL EXPRESSION OF La ANTIGENS

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In previous studies of murine Ia antigens, expression of these antigens in kidney could not be demonstrated. However, the recent demonstration of Ia-like antigens in rat and pig kidney and the probable importance of DR antigens in human renal transplantation encouraged us to reexamine the renal expression of murine Ia antigens, which are the prototype for all studies of Ia-like antigens. Using the sensitive technique of serial absorption, we were unable to demonstrate specific absorption of a polyspecific anti Ia.1, 2,3,7 serum by packed kidney tissue, in agreement with earlier findings. However, when oligospecific antisera against Ia.4, Ia.7, Ia.8, or Ia 9 were examined, specific absorption by kidney was observed. Such absorption was much less efficient than was absorption by spleen. The lack of absorption of the polyspecific anti Ia serum was apparently due to poor expression of Ia.1,2,3, in kidney, in contrast to the expression of other Ia specificities in kidney. Thus various Ia antigens may differ in their extent of renal expression, a fact which may account for some of the previous difficulty in demonstrating Ia antigens in renal tissue by absorption. Ia antigens were also shown to be immunogenic in mouse kidney: repeated immunizations of A.TL mice with A.TH kidney tissue produced a specific alloantiserum with anti Ia-like activity. Attempts to quantitate the amount of Ia in kidney relative to the amount of other antigens in kidney suggested that the amount of Ia was somewhat less than that of an H-2 specificity or of Ly-6.2, a non H-2 specificity with renal expression. We conclude that some (but perhaps not all) mouse Ia specificities are expressed in kidney in significant amounts and are immunogenic in kidney. These results support the hypothesis that Ia-like antigens could be important in human kidney transplantation, but raise the possibility of heterogeneity of Ia antigens in their extent of renal expression.

17. HLA 'HELPS' IMMUNE RESPONSE TO MINOR HISTOCOMPATILIBILITY ANTIGENS

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Little is known of the role of minor histocompatibility antigens in renal allograft rejection. On the one hand good survival associated with HLA identical sibling and zero mistmatched cadaver allografts suggests that HLA gene products play a major role in rejection. On the other hand the relatively poor (though significant) correlation which exists between graft survival and degrees of HLA-A, -B mismatch (0 to 4) suggests that minor incompatibility antigens may also play an important role as targets, especially in situations where they are accompanied by HLA mismatches. In this situation HLA antigens would function as helpers in the immune response to minor antigens.

This latter hypothesis has been tested using the Eurotransplant Data Bank. Three minor histocompatibility antigens namely H-Y, rhesus D and the blood group 'O' associated antigen were examined at 5 different levels of mismatch for HLA-A and -B antigens, namely 0, 1, 2, 3 and 4 antigen mismatches. Furthermore the data was divided into patients who had been presensitized and patients who had not been presensitized since it was known that a significant correlation between survival and HLA-A and -B mismatches is best seen in the presensitized group.

In the zero mismatched group no influence of minor histocompatibility antigens was detectable. However, with varying degrees of mismatch a strong influence of the minor histocompatibility antigens was observed and this effect was maximal as early as 6 months after transplantation. Thereafter no effect was detectable. This contrasted with the effect of HLA-A and -B antigens where a significant correlation between 0, 1, 2, 3 and 4 HLA-A, -B mismatches and survival is maximal at 24 months after transplantation.

Foreign gene products expressed in a renal allograft can be considered as having two functions, firstly a function as target for rejection and secondly a function as helper in the development of an immune response to other gene products expressed on the same cell surface. If interepreted in this light these data suggest that perhaps the major role of HLA antigens is as helper for the immune response to minor histocompatibility antigens. These data further suggest that, under the conditions of renal allografting with accompanying immunosuppression, minor histocompatibility antigens may be relatively weak helpers but are major targets for rejection in presensitized recipients.

18. USE OF MICROLYMPHOCYTOTOXIC TEST TO DEVELOP A CONGENIC MOUSE STRAIN FOR LY 6.2 ANTIGEN

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The microlymphocytotoxic test used for testing HLA-A, -B and -C antigens has been adapted for allo-immune sera raised in mice. In view of the non-specific toxocity of rabbit serum complement towards murine lymphocytes, the incubation period was shortened and the complement used in dilution of 1 : 8.

In order to raise antibodies against the Mls^{a}, a non-H-2 system controlling the mixed lymphocyte reaction, (BALB/c — Mls^{b} x CBA — Mls^{c})F$_1$ hybrids were injected with DBA/2 — Mls^{a} tissue. The antibody thus produced detected the 'DAG' i.e. DBA/2 antigen. Backcross studies indicated that it was controlled by a single genetic locus which segregated independently from H-2 and Mls.

A mouse strain congenic for DAG on a BALB/c background (BALB/c.DAG) has been developed by classical methods. Immunisation of (BALB/c x CBA)F$_1$ mice with this congenic strain produced an antiserum with identical reaction patterns to three sera raised in other strain combinations, all of which detect Ly 6.2.

DAG is present on more than 80% of peripheral blood, spleen and lymph hode lymphocytes as well as kidney and liver tissue.