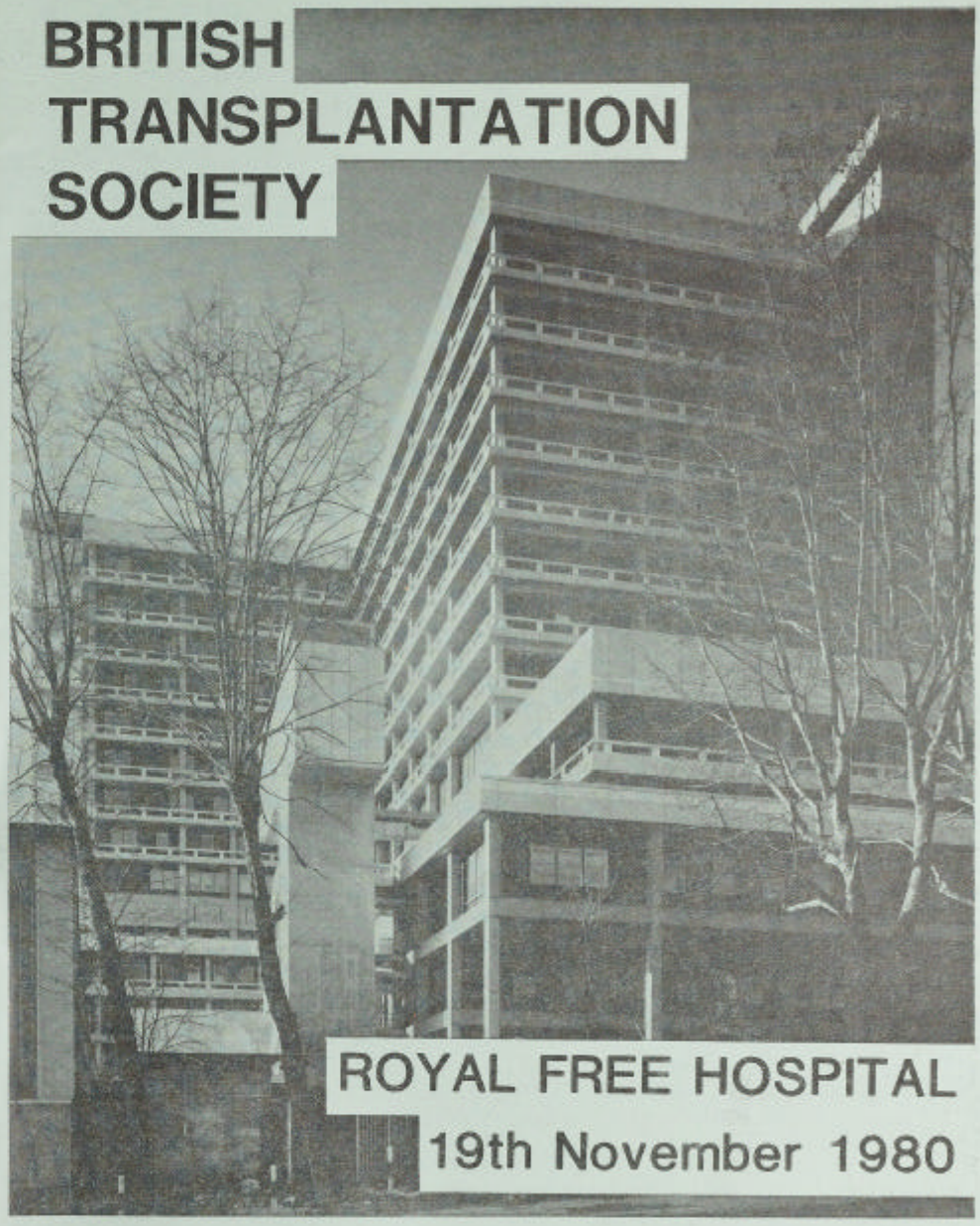
BRITISH TRANSPLANTATION SOCIETY



ROYAL FREE HOSPITAL

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ABSTRACTS....BOOKING FORM....SOCIETY BUSINESS

The dissemination of cytotoxic T cell activity in mucosal tissues following different routes of tumour administration.

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Using a newly developed technique, we have been able to produce large numbers of lymphocytes from the lamina propria of mouse small intestine. The high purity and viability of these lymphocytes has permitted a study of the cytotoxic T cell response to injected tumours. Following the intraperitoneal injection of P-815 ($H\text{-}2^d$) mastocytoma cells into $C_{57}Bl$ ($H\text{-}2^b$) mice, cytotoxic cells appear 5 days later in the lamina propria in quantities at least five times greater than that found in any of the organised lymphoid tissues, e.g. spleen and mesenteric lymph nodes. These high levels peak at around day 13 after injection and decline slowly with significant cytotoxic activity still being detectable at day 40. At all times, the cytotoxic response in the lamina propria exceeds that in organised lymphoid tissues. This observation is not peculiar to this system and has been demonstrated in other strains of mice injected with different tumours. Contamination of lamina propria cell suspensions by Peyer's patch lymphocytes can be ruled out as an explanation of high cytotoxicity since the latter cells exhibit a poor cytotoxic response. The cytotoxic cells generated in the lamina propria are specific for the immunising tumour and bear T cell markers. Analysis of lymphocytes from the lungs indicates that this early large cytotoxic response to tumours is a feature of cells in mucosal sites. Cytotoxic cells generated by subcutaneously injected tumour cells also have a propensity to localise in the lungs and to a certain extent in the lamina propria, rather than in organised lymphoid tissue. We would like to suggest that cytotoxic T cells preferentially develop in or localise in mucosal sites.

Transplantation of allogeneic bone marrow cells separated on a discontinuous albumin gradient into cyclophosphamide pretreated rats: induction of allograft tolerance.

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One of the most severe complications of allogeneic bone marrow transplantation in humans is the development of acute graft-versus-host (GVH) disease provoked by immunocompetent lymphocytes in the graft. One approach to prevent this condition involves the removal of the GVH-reactive lymphocytes by means of albumin density gradient centrifugation of the haemopoietic cell suspension (1).

We have applied this technique for the separation of rat bone marrow cell suspensions. The stem cells are concentrated up to 8 fold in fraction 3, however this fraction also contains a high concentration of cells responsive to PHA and histocompatibility antigens. Fractions from separated F344 bone marrow as well as unseparated cells were tested for their protective effect in WAG rats pretreated with 200 - 225 mg/Kg of cyclophosphamide. Injection of unseparated bone marrow cells (5×10^7/rat) resulted in 50% survival for greater than 60 days, while cells from fraction 3 (5×10^6/rat) gave 83% 60 day survival.

Recipients were tested for the presence of donor type lymphocytes in their peripheral blood using cytotoxic alloantisera. Temporary 'takes' were obtained in the majority of rats transplanted with whole bone marrow and permanent chimerism was found in less than 50% of survivors. Rats grafted with cells from fraction 3 showed permanent chimerism in 75% of rats tested.

Transplanted animals were tested for tolerance to donor antigens using skin grafts and reactivity in the mixed lymphocyte reaction (MLR). Rats in which reversion to host type haemopoiesis had been proven, rejected donor-type skin grafts and were not tolerant in the MLR. On the other hand animals with 50 - 80% donor-type lymphocytes retained donor-type skin for greater than 100 days and were tolerant in the MLR. The role of suppressor cells in the maintenance of this state of immunological tolerance will be discussed.

(1) Dicke et al (1969) Transplantation 8, 422 - 434.

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ARACHIDONIC ACID METABOLISM AND THE XENOGRAFT REACTION

The xenograft reaction in dogs has been studied by means of an extracorporeal in vivo xenohaemoperfusion system, grafting a monobloc preparation of a pair of cat kidneys on to a dog's arteriovenous shunt. In this model the course of the xenograft reaction has been studied in twenty experiments by the measurement of renal blood flow; arteriography; ultrasonic angiology; the measurement of arteriovenous gradients of red and white blood cells, platelets, clotting factors, immunoglobulins and complement across the xenograft; the measurement of A-V gradients of prostacyclin and thromboxane A_2 metabolites; and the gross and microscopical appearances of the xenografts, including the study of serial biopsies by light and electron microscopy. The reaction is characterised by phases of vasoconstriction followed by vascular obstruction associated with graft retention of platelets and release of thromboxane A_2. Graft renal blood flow may cease altogether after any of these phases of vasoconstriction and the reaction usually causes complete cessation of blood flow within 5 to 25 mins after revascularization.

In a further 40 experiments, arachidonic acid metabolism, which ultimately leads to thromboxane A_2 and prostaglandin production, was inhibited by pre-treatment of the recipient with either Methyl Prednisolone, (which prevents the release of arachidonic acid from membrane phospholipids), indomethacin (which inhibits the cyclo-oxygenase

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Enhancement of tumour allografts using TNP-modified alloantigen and anti-TNP serum

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Allogeneic tumours P815 ($H\text{-}2^d$) and EL-4 ($H\text{-}2^b$), injected s.c. into A strain ($H\text{-}2^a$) mice, were enhanced by alloantibody given i.p. at the time of transplantation. Likewise TNP-modified tumours were enhanced by anti-TNP serum. In both these models antibody can combine directly with antigens present on the cell surface (classical immunological enhancement). Unmodified P815 tumour was also enhanced by anti-TNP serum if TNP-modified Balb/c ($H\text{-}2^d$) membrane antigen was also given i.v. The effect was specific: TNP-Balb/c ($H\text{-}2^d$) antigen plus anti-TNP serum enhanced P815 but not EL-4 growth while TNP-C57Bl/6 ($H\text{-}2^b$) antigen plus anti-TNP serum had no effect on P815 growth but did enhance EL-4 growth. In the latter model the anti-TNP antibody cannot directly interact with the graft, so that the mechanism cannot be masking or modulation of foreign determinants. The mechanism most likely to account for the findings is antigen-reactive cell opsonization, for concurrent experiments have shown that alloantigen-reactive T cells specifically bind TNP-modified alloantigens and that, when cells which have bound such antigens are further incubated with anti-TNP serum and injected i.v. into normal syngeneic mice, they are taken up by the reticuloendothelial system.

These data have theoretical and practical implications. Firstly, the definition of immunological enhancement requires modification to include the role of complexes formed with antibody not reacting directly with the graft. Secondly, this approach has clinical appeal because a) TNP-modification of donor lymphocytes is quick and easy, b) only one serum would be required for all patients and c) the risk of hyperacute rejection would be entirely eliminated. Preliminary experiments with mouse skin and rat renal allografts are in progress.

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CONTINUOUS MONITORING OF RENAL TRANSPLANT FUNCTION BY EXTERNAL ARM COUNTING

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Reliable methods for detecting rapid changes in renal function are essential to optimum graft survival. In a study of 15 renal allograft recipients glomerular filtration rate (GFR) was monitored by external forearm counting using a sodium iodide crystal for the measurement of renal clearance of ^{99m}Tc(Sn) DTPA after an initial period of equilibration of the isotope within the tissues. This forearm counting method had previously been validated against standard methods of measuring GFR using radio-isotope techniques in 100 volunteers. Continuous measurements were made in the transplantees 5 - 24 hours daily for a period of 2 - 4 weeks following renal transplantation. The dose of isotope required was less than 1 mCi daily. Decrease in isotope clearance reflecting decreased GFR invariably preceded by 24 - 72 hours a rise in plasma creatinine levels in 17 episodes of biopsy proven rejection that occurred during the period of the study. Responses to treatment were also detected at a similar time interval prior to a fall in plasma creatinine. Transient changes in GFR caused by posture and mild exertion could be clearly differentiated from changes due to rejection. A miniaturised portable monitoring system using a cadmium telluride detector has now been evaluated in the same group of patients. The correlation between the cadmium telluride and sodium iodide detector systems is highly significant ($r = 0.89$). The rate of decay of radioactivity in the plasma correlates well with radio-isotope decay using both external detector systems. The cadmium telluride system has the advantage of being lightweight and portable thus enabling measurements to be made at the patient's bedside as well as allowing several patients to be monitored at the same time.

VIRUS INFECTIONS, T CELL SUBPOPULATIONS AND LYMPHOMA IN CYCLOSPORIN A TREATED RENAL ALLOGRAFT RECIPIENTS

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Over the past 36 months we have treated 19 patients with Cyclosporin A (CyA) initially in combination with azathioprine plus prednisolone and more recently with prednisolone.

Of these 19 patients 5 developed documented viral infections. Two developed typical infectious mononucleosis syndrome with a positive monospot test with no obvious sequelae. One patient developed a lymphoma containing Epstein Barr virus (EBV) nuclear antigen in over 90% of the tumour cells. This patient also developed a cytomegalovirus infection with viral inclusion bodies demonstrable on renal biopsy and has repeatedly exreted herpes simplex virus from his throat and urine.

The mode of action of CyA suggests that it acts against T cells. We have shown that both the absolute number and/or proportion of suppressor T cells is increased in patients on CyA. In addition we have shown that CyA promotes EBV induced B cell proliferation in vitro.

These two findings may explain the high incidence of serious virus infections in immunosuppressed patients and may help to explain the increased incidence of lymphomas in renal allograft recipients.

7 ACYCLOVIR FOR HERPES SIMPLEX INFECTION IN RENAL TRANSPLANT RECIPIENTS

Acyclovir (9- (2 hydroxyethoxymethyl) guanine, Acycloguanosine) is a chemically synthetised acyclic nucleoside with antiviral activity against viruses of the Herpes group. The drug was administered to five immunologically compromised renal transplant recipients with serologically proven Herpes simplex infection.

Two patients had a systemic illness with extensive lesions on the trunk and genitals. Two patients had oropharyngeal vesicals associated in one with a lesion on the nasal skin. In one patient, the lesions were confined to the skin of the cheek. Virus was cultured from mucocutaneous lesions in four cases each of whom had had unsuccessful preliminary treatment with Idoxuridine 5% in D.M.S.O.

Acyclovir was given as an intravenous injection over a period of two minutes. The recommended dosage in patients with normal renal function is 5 mg/Kg body weight every 8 hours. However, the drug is excreted by glomerular filtration and is probably also actively secreted through renal tubules. Patients with a creatinine clearance less than 30 mls per minute therefore received the drug at a reduced dose of 5 mg per Kg every 24 hours and those with a creatinine clearance between 30 and 80 mls per minute at a dose of 5 mg per Kg to avoid the danger of excessive accumulation.

This drug was found to be extremely effective in abolishing mucocutaneous lesions in these patients. There was no evidence of marrow toxicity at these dosage levels. Indeed, one patient successfully recovered from Azathioprine-induced bone marrow suppression while being treated. There was no significant adverse effect on liver function tests or measurable depression of renal function.

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CYTOMEGALOVIRUS INFECTIONS IN RENAL TRANSPLANT RECIPIENTS: POSSIBLE EVIDENCE FOR HLA-A1 RESTRICTED IMMUNITY TO GRAFTS IN THE PRESENCE OF CMV 8

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119 patients who received 133 renal transplants have been studied retrospectively for evidence of Cytomegalovirus infection (CMV) All grafts were implanted between 6 and 42 months prior to analysis. Serum samples taken before transplantation and at regular intervals thereafter were stored at -20°C. and assayed in batches using CFT and ELISA techniques. A four fold rise in CFT titres and ELISA values > 200 units indicated a CMV infection. Prospective screening of blood and kidney donors for CMV was not carried out. 86 (72%) patients were infected with CMV at or within three months of transplantation, and 33 (27%) remained negative.

Calculation of cumulative graft survival showed no difference between CMV positive (59% 1 year, 56% 2 years) and CMV negative (62% 1 year, 56% 2 years) recipients.

It has been found (ref.) that the development of cytotoxic T-cell responses to virus-infected target cells in vitro depend on the presence of antigens recognised as self being present on the target cell. We have looked for similar evidence of HLA restricted responsiveness in our CMV positive patients by calculating:

$$\frac{\text{Total numbers of each antigen found in the donors}}{\text{Total numbers of each antigen found in the recipients}} = D/R$$

and have compared D/R in failed graft recipients with D/R in successful graft recipients.

17 Antigens were common enough to enable statistical analysis; each antigen except HLA-A1 showed no significant difference in D/R between failed and successfully grafted patients. However D/R_{A1} in failed grafts was 1.0, but in successful grafts was 0.59 (χ^2=6.502, $p < 0.02$) No difference was found in D/R for any antigen in failed and successful grafts who were CMV negative.

This preliminary evidence suggests the possibility that HLA-A1 positive recipients receiving HLA -A1 positive donor kidneys may mount an immune reaction against the graft in the presence of CMV infection.

Ref: DOHERTY PC BLANDEN RV ZINKERNAGEL RM: (1976)
Transplantation Reviews 29:89

9 IMMUNOGENICITY OF RAT KIDNEY ALLOGRAFTS

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The failure of long surviving (ASxAUG)F_1 kidney transplants to induce T-dependent primary alloimmune responses when retransplanted into second AS recipients has previously been demonstrated. The probable explanation is that the stimulus for primary T-dependent immunity of kidney allografts is provided by passenger cells. We wish now to identify which of the passenger cells (intra and/or extravascular) is responsible.

An estimate using ^{51}Cr labelled red cells was made of the volume of blood remaining in a donor kidney drained of as much blood as in our procedure. The results showed that 0.1ml of blood was retained in a kidney. Retransplantation experiments of long surviving (ASxAUG)F_1 kidneys into second AS recipients were then performed, and varying amounts of (ASxAUG)F_1 cells were injected I.V. at the same time.

The results, (Table) suggest that the intravascular passenger cells are unlikely to be the major primary immunogenic stimulus. The initial experiments with plastic adherent spleen cells indicate that they can provide an immunogenic stimulus.

TABLE

CELLS INJECTED AT RE-TRANSPLANTATION	SURVIVAL TIME OF 2nd RECIPIENT (days)
0.1ml blood	29, 100, 100, 100
0.5ml blood	12, 12, 100, 100
2 x 10^6 ASxAUG (PASC)	10, 10, 11, 24 (s)
5 x 10^5 ASxAUG (PASC)	10, 17(s), 22 (s)
No cells	100, 100, 100, 100

FUNCTIONAL STUDIES IN 6 DAYS SUCCESSFUL PRESERVED CANINE KIDNEYS. 10

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To make more time consuming advanced immunologic donor - recipient matching possible, a new method to extend the preservation time of kidneys was investigated. In 6 mongrel dogs the right kidney was removed, flushed with a Collins solution and then perfused in a Gambro preservation machine for 6 days. This period of hypothermic continuous perfusion was interrupted halfway through by three hours normothermic ex vivo perfusion on the same donor dog. After 6 days autotransplantation was performed followed by contralateral nephrectomy. In a control group of 6 dogs the kidneys were continuously preserved in the Gambro machine during 6 days. In the ex vivo perfused group all animals survived after autotransplantation; in the control group only one out of 6 dogs survived.

During the 3 hours ex vivo perfusion and one hour after implantation the glomerular filtration rate (GFR), the effective renal plasma flow (ERPF) and the filtration fraction (FF) were calculated from clearances of ^{125}Iothalamate and ^{131}I hippuran respectively. The beneficial effect of the normothermic ex vivo perfusion halfway through the preservation period could be demonstrated during this procedure. Based on hourly measurements of GFR, ERPF and urine output an improving proximal tubular secretion and water reabsorbtion was observed during the ex vivo perfusion. A low FF (<0.26) measured one hour after implantation correlated well with, and predicted life sustaining kidney function.

These results show that that it is possible to restore a 3 days preserved kidney by a relative short period of normothermic ex vivo perfusion after which the organ can be preserved for another 3 days. We currently investigate whether the normothermic perfusion can be performed with identical results using a heart-lung machine. This procedure might provide the possibility for both monitoring of damaged organs and long term kidney preservation.

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MODIFICATION OF GRAFT SURVIVAL IN THE RAT BY TRANSFUSION OF THE DONOR.

We have evidence that immunisation of the donor modifies graft survival in rat, dog and man, which suggests that elements other than antigen recognition may be involved in the allograft reaction. In the rat a 3rd party bloodtransfusion to the donor the day before transplantation reduced heart and kidney graft survival significantly. Transfusion of Wag/Rij recipients with BN donor blood induces permanent heart graft survival (group II), which could be reduced to control survival times in 3 out of 5 animals by donortransfusion. Transfusion of donorblood to the recipient in the Wag/Rij to BN combination induced accelerated rejection (group V), which was more pronounced after 3rd party bloodtransfusion of the donor (group VI). Kidney graft survival was also significantly reduced in non-transfused Wag/Rij recipients by treatment of the BN donor with 3rd party blood (group VIII). In contrast, donor pretreatment with recipient cells induced prolonged survival (groups IX, X). This interesting observation that donor pretreatment with 3rd party cells has an effect opposite to donor pretreatment with recipient cells suggests that the effect of donor transfusion may be an immunological phenomenon.

Group	Donor	Transfusion	Recipient	No.	Grafts	Mean Survival Time
I	BN	-	Wag/Rij	25	heart	all 8-9 days
II	BN	-	Wag/Rij + 2 ml donor blood	25	heart	permanent survival
III	BN	3rd party blood	Wag/Rij + 2 ml donor blood	5	heart	7,8,10, >100, >100
IV	Wag/Rij	-	BN	25	heart	all 8-9 days
V	Wag/Rij	-	BN + 2 ml donor blood	25	heart	5,5,5,5, etc. (25x)
VI	BN	3rd party blood	BN + 2 ml donor blood	5	heart	3,3,3,4,4
VII	BN	-	Wag/Rij	8	kidney	8,8,8,8,8,8,8,9
VIII	BN	3rd party blood	Wag/Rij	8	kidney	5,6,6,6,6,7,7,7
IX	BN	recipient lyc.	Wag/Rij	10	kidney	9,10,10,10,10,11,12,12, 13,18
X	BN	recipient lyc. (4 inj.)	Wag/Rij	7	kidney	11,12,12,12,13,16,21

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Successful autotransplantation of fresh and cryopreserved porcine islets of Langerhans

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One of the main problems with islet transplantation in man and in large animals is that the volume of harvested islets has been too small.

In this study a simple method of collecting pancreatic islets by mechanical dissociation followed by filtration through nylon mesh has been adopted. Enzyme digestion has been avoided.

In vitro production of insulin with this preparation has been excellent. Viability of the islets has been tested by intrasplenic autotransplantation in the diabetic pig of fresh and cryopreserved islets stored in DMSO at -196°C for 7 days. The pigs were rendered diabetic by intravenous injection of streptozotocin.

Group I - Fresh islets

Four out of 5 pigs remained normoglycaemic after streptozotocin and graft injections. Spleens were removed after 10 days causing all 4 pigs to become diabetic. The fifth pig died of splenic infarction.

Group II - Cryopreserved islets

Four out of 5 pigs became normoglycaemic with monitored output of insulin and C peptide. All 4 returned to the diabetic state after splenectomy at 10 days. The fifth became normglycaemic but did not return to the diabetic state after splenectomy.

In conclusion, control of blood sugar has been achieved in large animals by autotransplantation of pancreatic islets.

Pancreatic islets functioned well after cryopreservation.

13 [illegible] ALLOGRAFT REJECTION BY COMPUTER

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Computers can be used to store data and to present it later either in tabular or graphical form. Statistical analysis can be incorporated in the presentation to aid decision making. In transplant recipients it is often appropriate to compare sequential results not with a "normal range" but with the previous trend observed in the same patient.

Statistical methods based on Bayes Theorem can define trends in a sequence of results, reflecting either improvement, deterioration or stability, and can express the probability that a new trend is developing. When a result becomes available it is possible using this approach to determine whether the previous result showed 1) a continuation of the previous trend; 2) a transient change (e.g. laboratory error); 3) a change in level (e.g. after dialysis) or 4) a change in slope (e.g. a change in renal function as a consequence of rejection), and so determine the probability that the new result represents a significant change.

A computer programme has been developed which detects changes in slope, and filters out changes of little clinical concern such as improving function, laboratory error and level changes due to dialysis. The sensitivity of the system is governed by the total variance in the data. The programme automatically responds to changes in variance due to the laboratory assay, to variation in the timing of sample collection and to truncation of numerical results.

Sequences of creatinine and urea results from 28 patients over the 60 days after transplantation were analysed. The computer identified prospectively all episodes considered, by subsequent clinical review, to be allograft rejection. The method provides an objective assessment of the time of onset of a change in the trend of serum creatinine results, which should be useful as an alerting system in clinical practice, and could add objectivity to studies of rejection in transplant recipients.

SERIAL SCANNING OF RENAL TRANSPLANTS IN THE CLINICAL CONTEXT. 14

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The progress of renal transplants has been assessed serially using radioiodinated hippuric acid (Hippuran). A number of diagnostic indices have been evaluated against clinical data.

Each of thirty patients has been studied within twenty-four hours of transplantation, then at forty-eight hour intervals up to ten days and thereafter when clinically indicated. Gamma Camera renography was performed using a calibrated dose of 1.8-2.8 MBq I^{131} Hippuran or 3.7 MBq I^{123} Hippuran. The effective renal plasma flow was measured at the same time using a single sample technique.

The percentages of the dose in the kidney and bladder were estimated from the derived curves with and without background correction. These figures have been compared with the clinical and biochemical data to assess which parameter is the most sensitive indicator of early rejection and which is best for following the kidney's progress through a rejection episode.

Deterioration in the radiorenogram was a very reliable indicator of early rejection particularly when renal function was insufficient to maintain the patient without dialysis. Effective renal plasma flow was not always an accurate indicator of renal function. However serial estimation of both parameters together gave clear indication of graft progress or decline following acute rejection, and were therefore useful aids in preventing the unnecessary use of immunosuppresive therapy.

15 PROPERDIN FACTOR B (Bf) AND KIDNEY GRAFT SURVIVAL

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The gene coding for the properdin factor B(Bf) component of the alternate complement pathway has been mapped between the HLA-B and HLA-DR loci. There are 4 allotypes of Bf: two common ones BfS and BfF and two rare ones BfF1 and BfS1.

The role has been studied of the Bf locus in graft survival (g.s.) in 39 patients who received their first transplant between January 1978 and March 1980 in Manchester. All patients whose kidney donor's serum was available were included. The overall g.s. at 6 months was 61.5%. This is comparable with the g.s. of 59.9% at 6 months for all 116 patients who received first transplants during the same period.

G.s. at 6 months for patients who received a kidney from a Bf identical donor was 73.9% compared with 45.4% in patients who received a kidney from a Bf incompatible donor. Patients receiving a graft from a Bf compatible donor (e.g. donor BfS, recipient BfFS) had a g.s. of 67.8%. The best g.s. was seen in the group of 16 BfS patients who received a graft from a BfS donor (81.2%). Although the differences in g.s. are not statistically significant, there is a trend towards better g.s. in patients receiving a graft from a Bf compatible or identical donor. A study in a larger series of patients is required.

The possible role of the Bf locus will be discussed and a detailed analysis of the HLA antigen matching in various Bf groups will be discussed.

Group	No. patients	Func. grafts (6 months)	
Overall	39	24	61.5%
Bf compatible	28	19	67.8%
Bf incompatible	11	5	45.4%
Bf identical	23	17	73.9%
Bf BfS	16	13	81.2%

16 A PROSPECTIVE RANDOMISED TRIAL OF AN "ENHANCING" ANTISERUM USED PROPHYLACTICALLY TO PREVENT REJECTION: PRELIMINARY RESULTS

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Despite the improvement in the results of renal transplantation in man resulting from wider use of blood transfusions, there is still an unsatisfied need for a non-toxic immuno-suppressive agent.

In mice, alloantisera retaining anti-Ia activity after absorption of anti-SD activity by platelets, suppress skin graft rejection without evidence of antibody mediated damage occurring. (ref.)

A similar reagent was prepared in man: 14 group A healthy blood donors were paired and immunised against each other. Plasmaphoresed serum was absorbed in batches against a panel of platelet donors, sterilised and stored at -70°C. after extensive evaluation for safety.

A prospective randomised blind controlled clinical trial was initiated in cadaver renal graft recipients in April 1978 the experimental group (n=15) received 80 ml serum I/V on the day of transplantation and on day 1, 3, 5, and 7 thereafter 20 Controls received a placebo. Medical staff did not know which patients belonged to which group during treatment.

Results: No side effects directly attributable to the serum were seen. 2 patients died, one in each group. The cumulative graft survival in the experimental group is 20% eighteen months post transplant compared with 65% in the control group ($p < 0.05$) These results will be discussed.

Reference: STAINES NA GUY K DAVIES DAL (1975)
Eur. J. Immunol. 5 782