MEETING OF

THE BRITISH TRANSPLANTATION SOCIETY

16th July, 1975

Lecture Theatre 2,
University Hospital of Wales, Cardiff

10.45 a.m.	COFFEE
11.10 a.m.	Welcome
11.15 a.m.	T.H. Dunningham and J.E. Castro (Urology and Transplant Unit, Royal Postgraduate Medical School, London): 'Leucocyte migration as a predictive test of acute rejection of kidney transplants'
11.30 a.m.	D.E. Osborn and J.E. Castro (Urology and Transplant Unit, Royal Postgraduate Medical School, London): 'Inhibition of the M.L.C. by serum factors and their effects on human renal allograft survival.'
11.45 a.m.	T.H. Dunningham and J.E. Castro (Urology and Transplant Unit, Royal Postgraduate Medical School, London): 'A study of the use of radioactive fibrinogen in the prediction of acute rejection of human renal transplants.'
12 noon	A.M. Godfrey and J.R. Salaman (KRUF Institute of Renal Disease, Cardiff): 'The role of radiotherapy in the treatment of acute renal transplant rejection.'
12.15 p.m.	J.C. Hammonds and M. Fox (Renal Transplant Unit, Royal Hospital, Sheffield): 'Urinary fistula after renal transplantation - report on 27 cases.'
12.30 p.m.	Yvonne Mangnall, A. Smythe, D.N. Slater and M. Fox (Renal Transplant Unit, Royal Hospital, Sheffield): 'Experiences with transplantation of Islets of Langerhans.'

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A B S T R A C T S

(not for publication)

T.H. DUNNINGHAM and J.E. CASTRO

The object of this study was to assess the value of the leucocyte migration test (L.M.T.) as a predictive test of acute rejection of kidney transplants. The L.M.T. modified from Smith (1969) was used with donor specific antigens from lymph node or peripheral blood leucocytes. Inhibition of migration (index <73%) was derived from the mean index for normal controls (100% ± 2.5 S.E. S.D. 13.5) less 2 S.D.

$$100 - 2 \times 13.5 = 73$$

350 tests were performed at regular intervals on 27 patients with functioning transplants up to 6 months after transplantation. Acute rejection episodes were diagnosed by conventional clinical criteria and without reference to the L.M.T.

63 acute rejection episodes were diagnosed. Only 6 were correctly predicted by a positive L.M.T. in the 5 days prior to the onset of rejection; 47 episodes were preceded by negative tests.

Of 41 positive tests, 23 were followed by acute rejection episodes within 1 to 36 days (mean 13.3 days) and 18 were not followed by acute rejection.

The mean index of 73 tests performed in the 5 days prior to rejection episodes was not significantly different from the mean of 167 tests during stable graft function with basal immunosuppression.

We conclude that the L.M.T. is of no value in the prediction of acute rejection episodes.

SMITH, M.G.M. et al, Brit. Med. J., 4, 275 (1969)

D.E. OSBORN and J.E. CASTRO

Human renal allograft survival may be influenced by circulating humoral factors. Serum from recipients of successful live donor renal transplants and patients undergoing cadaver transplants was examined for factors which inhibit mixed lymphocyte culture (M.L.C.).

Inhibition of M.L.C. was measured in a one way culture by substituting 20% of test serum for control AB serum. In each experiment six combinations of recipient and unrelated mismatched lymphocytes were studied. Significant inhibition was recorded if the ratio of transformation in control and test cultures was at least 2.5. Inhibition was not found in any of ten patients who had undergone successful live donor transplantation at least six months previously.

In 8 patients with successful cadaver transplants serum was tested in 4 before operation. Inhibition of M.L.C. was present in one patient and in only 3 of 24 combinations. Serum taken after transplantation caused inhibition in 4 of 7 patients but only 4 of 42 lymphocyte combinations.

In 6 patients in whom 8 cadaver kidneys were rejected, serum tested for M.L.C. inhibition before 7 transplants showed inhibition in all of the patients and 22 of 42 lymphocyte combinations. Serum taken after transplantation caused inhibition in 7 of 9 patients and in 21 of 48 combinations.

These observations suggest that humoral factors which cause inhibition of the M.L.C. are unnecessary for continued function of successful live donor transplantation and their pre-existence is associated with a significantly increased incidence of rejection of cadaver transplant.

T.H. DUNNINGHAM and J.E. CASTRO

Yeboah et al (1973) described a method of diagnosing acute rejection in human renal transplants consisting of daily scintillation counts over the heart and transplant. It was claimed that when the ratio

$$\frac{\text{counts over transplant}}{\text{counts over heart}} \times \frac{100}{1}$$

exceeded 120% this indicated deposition of fibrin in the transplant implying impending rejection.
Further study of this method has been made with daily counts from the 7th to 28th days inclusive. 34 patients were studied and an average 14.6 readings taken from each. 13 patients had acute rejection episodes diagnosed by conventional clinical criteria and without reference to the fibrinogen test. The mean transplant/heart ratio was determined for the 5 days prior to the rejection episode and compared with the mean for the period when the transplant function was stable and the patient was receiving basal immunosuppression. Pre-rejection figures were 105.6% $\pm$ 11.3 and stable function figures 99.7% $\pm$ 6.1 but the difference was not significant. Similarly, the incidence of ratios over 120% was not significantly higher (25%) for the pre-rejection phase than for the phase of treatment of rejection (22.5%) or for the phase of stable function (26.4%).

Former claims for the ability of this method to predict acute rejection have not been substantiated.

YEBOAH, E.D., CHISHOLM, G.D., SHORT, M.D., and PETRIE, A.
Brit. J. Urol., 45, 273 (1973).

A.M. GODFREY and J.R. SALAMAN

Radiotheraphy has been used for many years as part of the routine treatment for acute renal allograft rejection. However its efficacy has never been tested in a controlled clinical trial. From July 1972 all patients transplanted at the Cardiff Royal Infirmary and who suffered a rejection episode were entered into a trial. They were randomly allocated to a group receiving standard rejection therapy (intravenous Solumedrone 1. gram. 12 hourly for three doses, repeated after 4 days if no response was obtained), and a group receiving radiotherapy to the graft in addition (4 doses of 150 rads. on alternate days). Maintenance doses of Azothiaprine and Prednisone were continued in both groups. Patients of both sexes and those receiving living and cadaver grafts were equally distributed between the two groups. A total of 40 rejection episodes have been studied. Two weeks after rejection was instituted creatinine levels were lower in the radiotherapy group. However by four weeks there was no marked difference and the ultimate transplant survival was the same (40%). We conclude that radiotherapy to a rejecting renal transplant confers no benefit to the patient.

J.C. HAMMONDS and M. FOX

Urinary fistula following renal transplantations has in the past heralded a grave outcome for most patients. This has not been our experience and for this reason management and prognosis of 27 fistulae which occurred in 117 patients has been reviewed. In addition the steps taken to prevent the condition in more recent cases are described. 27 urinary fistulae occurred following 117 consecutive renal transplants. In the majority (23) the fistulae originated from the cystostomy or ureteroneocystostomy sites, but 4 arose from the pelvis or renal substance. The leak became apparent one to 68 days after operation. Treatment was initially conservative by urethral catheter drainage, and if rapid closure did not occur, attempts were made to define the origin by I.V. indigo carmine, methylene blue instillation, I.V.P. and cystography. Fistulae arising from the lower tract were treated by prolonged continuous catheter drainage for periods varying from 3 to 92 days and 20 out of 23

eventually closed. One patient in this group died and transplant nephrectomy was performed in the other two. Upper tract fistulae occurred in 4 patients as a result of localised vascular injury or spasm. Leakage continued until dealt with operatively, with removal of necrotic tissue, closure of the defect and reinforcement by an omental patch in two and late nephrectomy in the other two. In the recent 22 transplants the incidence of lower urinary tract fistulae was reduced to 2 by using chromic instead of plain catgut for the ureteroneocystostomy and meticulous 3 layer bladder closure with chromic catgut and Dexon. There were six deaths in the series (22%) but in only 3 could death be directly related to the fistula. Two of these had leaks from the upper tract. The overall mortality was no higher than that in the total number of transplants.

A number of previous reports of a high mortality from urinary fistulae were thus not substantiated. Prolonged catheter drainage if performed with rigid aseptic precautions was the treatment of choice for lower tract fistulae, while early operative intervention is recommended for leaks from the upper tract.

YVONNE MANGNALL, A.SMYTHE, D.N. SLATER and M. FOX.

Transplantation of the pancreas for the treatment of diabetes has been recorded in 35 patients but very high mortality has made more widespread application unjustifiable. Only two patients have survived for over two years with return to normoglycaemia.

Transplantation of isolated islets of Langerhans in the free state has therefore been explored as a safer alternative and the results we have achieved over the past three years are reported. The rat was used as the experimental model. The aims were to: 1) Isolate islets of Langerhans from the pancreas in adequate numbers; 2) confirm normal morphology by light and electron miscroscopy and insulin production in vitro; 3) establish satisfactory transplantation sites and prolonged survival in isogeneic recipients; 4) return rats made previously diabetic by streptozotocin to a normoglycaemic state and study the metabolic and histological changes after transplantation.

Collagenase digestion was used for the isolation of islets of Langerhans in the adult rat (Thomas, Grieve and Fox 1973) and in the neonatal animal (Leonard, Lazarow and Hegre 1973). A yield of approximately 250 islets is obtained from an adult pancreas. The islets appear normal on microscopy with granulated beta cells, and insulin is secreted on stimulation with glucose. Transplantation has been established under the capsule of the kidney, in the testis, intraperitoneally and following injection into the portal vein. The diabetic state has been reversed within one week following intraperitoneal injection of neonatal islets with weight gain, loss of polyuria and glycosuria and attainment of normoglycaemia. A minimum of 100 mg. pancreatic tissue is required for this effect, which shows no evidence of reversal after five months. In allogeneic combination the islet tissue is antigenic with rapid immunological rejection in the unmodified recipients.

LEONARD, R.J., LAZAROW, A., HEGRE, O.D., Diabetes 22, 413, 1973.
THOMAS, D.R., GRIEVE, A.A. and FOX, M., Nature, London 242, 258, 1973.

PAULINE F. BOYLE, M. FOX and D. SLATER

Previous work has shown that suspensions of testis homogenates can be transplanted in autologous and isologous combinations in the mouse with survival and function of interstitial cells (Fox and Boyle 1973). The aims of the present investigations were to determine

1) the most effective site for transplantation.
2) the minimum quantity of graft needed for physiological action.
3) the effect on the graft and on its action of varying periods of ischaemia, at body and room temperature, and preservation at 0-4°C.

Autologous transplantation was performed in inbred mice to subcutaneous (ear lobe, dorsum of trunk, snout) and intra-peritoneal sites by the method previously described. Results were assessed by seminal vesicle and penile weights, histological appearance of the grafts and plasma testosterone levels 3 months after grafting.

Following castration of 3 weeks old mice, seminal vesicle and penis development did not occur; and castration in the adult animal resulted in seminal vesicle and penis atrophy. However, after transplantation, seminal vesicle and penile weights approached those of sham operated control animals. Intra-peritoneal implantation produced maximal effects and as little as 20mg. of testicular tissue could be grafted with demonstrable androgenic action on the host. Testes were removed, homogenised and stored in tissue culture medium 199 over periods of ½ to 48 hours at 37°C, room temperature (20°C) and 0-4°C, and thereafter injected back into the same animal subcutaneously. Interstitial cells were shown to survive and function after 48 hours' preservation at 0-4°C and 12 hours at 20°C, but did not survive 4 hours at 37°C.

FOX M. and BOYLE P.F. Brit. J. Urol. 45. 696-701.