

- 11.45 a.m. ~~E. N. Wardle, P. R. Uldall and J. Swinney (Royal Victoria Infirmary, Newcastle-upon-Tyne):~~
Cancelled Radiofibrinogen catabolism studies in renal allograft recipients.'
- 12 noon M. Anderson, P. Dewar, L. B. Fleming, P. M. Hacking, A. R. Morley, S. Murray, J. Swinney, R. M. R. Taylor, P. R. Uldall and E. N. Wardle (Royal Victoria Infirmary, Newcastle-upon-Tyne):
'A controlled trial of dipyridamole in human transplantation and an assessment of platelet function studies in rejection.'
- 12.15 p.m. M. Fox, C. Bransom, K. Gelsthorpe and L. Henry (Renal Transplant Unit, Royal Hospital, Sheffield):
'A trial with preparation of goat ALG and its use in renal transplantation.'
- 12.30 p.m. A. D. Barnes and K. Hofmann (Renal Unit, Queen Elizabeth Hospital, Birmingham):
'A controlled trial of ALG in cadaveric renal transplantation.'
- 12.45 p.m. ~~E. N. Wardle (Royal Victoria Hospital, Newcastle-upon-Tyne):~~
Cancelled 'Use of an endotoxin assay in renal transplant recipients.'
- 1.00 p.m. LUNCH.
- 2.00 p.m. BUSINESS MEETING OF THE SOCIETY.
- 2.15 p.m. SYMPOSIUM ON 'KIDNEY DONORS'—organised by J. R. Salaman.
'The donor card'—Desmond Browne, Legal Correspondent to the British Medical Journal.
'Procurement of kidneys'—G. P. Alexandre, Professor of Surgery, Louvain, Belgium.
R. D. Weeks, Consultant Neurosurgeon, Cardiff.
- 3.25 p.m. TEA.
- 3.40 p.m. to 5.15 p.m. WORKSHOP ON 'HEART AND LIVER TRANSPLANTATION'
—organised by R. Y. Calne.
'Clinical and experimental heart grafting'—P. Caves, Edinburgh.
'Selection of patients and overall results of clinical liver transplantation'
R. Williams, London.
'Surgical aspects experimental background of liver transplantation'
R. Y. Calne, Cambridge
'Biliary composition after transplantation'—R. P. L. Waldram, London.

GENERAL NOTICES

Access to Wellcome Building

The nearest underground stations are Euston, Euston Square and Russell Square.

Future Meetings

16th OCTOBER, 1974—Autumn Meeting, Wellcome Building, London.

3rd JANUARY, 1975—in Cardiff.

16th APRIL, 1975—Joint meeting with Société Française de Transplantation, Wellcome Building, London.

ABSTRACTS (not for publication)

J. J. Keuning, A. Termijtelen, J. G. van den Tweel and J. J. van Rood

This paper describes the recognition of MLC determinants by MLC testing with lymphocytes of HL-A and MLC homozygous offspring from consanguineous marriages. We call these lymphocytes "typing cells."

We tested a panel of 58 normal panel donors in the MLC test with 7 different typing cells, using the typing cells as stimulator cells. Of the 58 panel donors, only 3 showed a negative reaction, all against the same typing cell, and another 5 panel donors showed weakly positive reactions against 3 different typing cells. In these cases of negative or weakly positive reactions there was a striking similarity between panel donor and typing cell as far as the antigens of the Four series were concerned. The results, indicating a high polymorphism of the MLC locus (i) in man and a linkage disequilibrium between some HL-A antigens and some MLC determinants, will be discussed.

P. J. Dewar, Sheila Murray, P. R. Uldall, R. Wilkinson, D. N. S. Kerr, R. M. R. Taylor and J. Swinney

The results from one centre of eighty-two cadaver donor first renal transplants have been reviewed. The minimum follow-up was six months post-transplant.

Eleven failures were considered to be unconnected with rejection or its treatment. One case was not included in certain analyses because no donor lymphocytes were available for testing. Seventy-one cases are therefore available for analysis.

The findings confirmed the significant benefit of second locus two-antigen identity matching reported by Oliver *et al* 1972*. Seventeen out of twenty cases with identity at the second locus had good functioning grafts compared with twenty-eight out of fifty cases in the non-identical group ($P < 0.025$).

Pre-transplant blood transfusion had a beneficial effect on kidney survival. Thirty-six out of forty-six transfused patients had surviving kidneys compared with eleven out of twenty-five non-transfused patients ($P = 0.001$).

Preformed cytotoxic antibody was present in eight patients but in no case was the antibody reactive against the donor lymphocytes. All eight had good functioning kidneys compared to thirty-seven of sixty-two patients without antibody ($P = 0.025$).

A significant association was found between the Rh(D) group of the recipient and the clinical outcome. Forty-one out of fifty-six Rh(D) positive recipients had good function compared with only four out of fifteen Rh(D) negative recipients ($P = 0.001$).

* Oliver, R. T. D.; Sachs, J. A.; Friesenstein, H.; Pegrum, G. D., and Moorhead, J. F. (1972) *Lancet* **ii** 1381.

J. G. van den Tweel, H. M. Vriesendorp, D. L. Westbrook and J. J. van Rood

In dogs, like in men, there appear to exist a major histocompatibility complex (DL-A) consisting of at least three different genetic systems. Two are definable by serological methods (the SD₁ and SD₂ system) and one has to be studied in the MLC test (the LD system). Although the important influence of the complex as a whole in transplantation procedures is widely accepted, the separate roles of any of the three constituent systems remain to be analysed.

To allow an experimental evaluation of the effect of these SD and LD structures in an outbred animal, we studied the LD system in the dogs. Our results can be summarized as follows:

1. In the dog an LD locus separate from the known SD loci is located on the chromosome nearer to SD₁ than to SD₂ and outside the SD region;
2. The LD system is highly polymorphic;
3. There is a strong linkage disequilibrium between the SD₁ and the LD locus in the dog. As this linkage disequilibrium is stronger than that found in man, it can explain the good results of organ transplants in SD identical unrelated dogs;
4. The recombination frequency between the SD and LD loci is low.

Elizabeth Simpson, Susan O'Hopp, M. Harrison, D. Mosier, K. Melief and H. Cantor

Balb/c and C57Bl/6 mice, when injected neonatally with (C57Bl/6x Balb/c)F lymphoid cells at birth develop a disease characterized by runting and splenomegaly. The lesions found in lymphoid organs are initially proliferative, involving cells in both T and B areas, but subsequently there is almost total replacement by reticulum cells. In late stages, liver and lungs are also infiltrated with reticulum cells. Studies of *in vitro* lymphocyte function at various ages indicate an impairment of all T cell functions: MLR and cytotoxic responses both to antigens present on the F cells, and to third party antigens, are either absent or depressed and PHA and Con A responses are below normal. The mice are chimeras for at least the first 2 to 3 months of age, since immunoglobulin allotype characteristic of the F cells is found in their sera. The disease probably can be attributed to a chronic host-versus-graft response.

P. Stewart, A. E. Thompson, and J. Swinney

Rejection of allografts is associated with a marked lymphocytic infiltration. Quantitation of the latter provides a useful method of measuring the reaction and may be used for assaying agents which possibly produce immunosuppression by reducing this infiltration.

Using a trephine, a circumcised was made into the decapsulated donor kidney; the base was then amputated, leaving a disc of uniform size.

Incision and elevation of the recipient capsule allowed the disc to be placed with its decapsulated surface in contact with the renal cortex of the recipient. Microscopy of stained paraffin sections of 7 and 10 days autografts and isografts showed the tubules of the graft touching those of the recipient kidney, but with negligible evidence of cellular infiltration in the junctional zone of the graft.

In contrast, older allografts, transplanted under controlled immunogenic conditions across a strong histocompatibility barrier, displayed a marked band of lymphocytes in the junctional zone of the graft.

Using an eyepiece graticule, 'blind' lymphocyte counting was carried out in 230 grafts. Analysis of the results showed:

1. No difference between autografts and isografts ($p=0.3$).
2. A highly significant difference between autografts and allografts ($p=0.001$).
3. A highly significant difference between azathioprine and prednisolone treated allografts compared with controls ($p<0.001$).
4. Female CBA mice reacted more vigorously than males ($p<0.01$).
5. The time of maximum lymphocytic infiltration was sex dependent, occurring in females on day 11 and males on day 9.
6. Reversal of the donor recipient relationship produced a greater reaction for the BALB/C hosts ($p<0.01$).

Provided the lymphocytic infiltration is accepted as a measure of the graft reaction then one has a sensitive technique for assaying immunosuppressive agents which act by inhibition of lymphocyte mitosis or by lymphocytolysis and evaluating tests which measure histocompatibility differences.

J. M. Crosland, A. D. Barnes, J. D. Blainey, D. B. Brewer, P. Dawson-Edwards, M. L. Oheid and B. H. B. Robinson

Biopsies from 160 kidneys transplanted between 1968 and 1973 were examined by one experienced pathologist.

Sixteen biopsies contained fibrin deposits in glomerular capillaries and 12 were first transplants, 3 were second and 1 was a third transplant.

Fourteen patients were involved. Two patients had deposits on biopsies of two transplants: one of these two patients received an HLA identical kidney at each operation and rejected the first but did well after the second. The other patient had deposits in his second and third transplants and died later.

Eight transplanted kidneys were removed after an average of 18 days. The remaining 8 kidneys functioned but three patients died at 3, 12 and 14 months of causes unrelated to rejection, leaving 5 patients alive and with good renal function.

Frequency of deposits was: 10% in first transplants; 20% in second transplants; 25% in third transplants. Patients alive at 20-12-73:

- 1st transplant, with deposits 50%, whole series 50%;
- 2nd transplant, with deposits 33%, whole series 50%;
- 3rd transplant, with deposits 0%, whole series 50%.

Other data analysed includes basic disease, sex ratio, parity, antibodies, ischaemic and anuric times.

Posting, blood transfusion, immediate urine production did not help distinguish these from others in the whole 160 biopsies
9 of 16 exam polys in slide

R. F. M. Wood, Aileen C. Gray, S. G. Packer, P. R. F. Bell and Pamela M. Pitcher

The detection of rejection in human cadaver kidneys using fibrin/fibrinogen degradation products (FDP) is frequently complicated by a degree of acute tubular necrosis. This tends to cause high and rather variable results in the first two weeks after transplantation.

This study was undertaken to establish the predictive value of urinary FDP in rejection when compared to biochemical estimations, in an experimental situation with zero warm ischaemic time.

A reliable method for measuring FDP in dog urine was established using a modification of a commercially available human tanned red cell haemagglutination inhibition test (Wellcome Reagents Ltd.). Consistent results were achieved by using a specific rabbit anti-dog fibrinogen serum and the human fibrinogen sensitised sheep cells from the test kit as an indicator. This system gave an assay with a sensitivity of 5µg/ml.

Twenty-five urine samples from normal dogs were tested and all had undetectable levels of FDP. A series of 12 renal transplants were performed, exchanging kidneys between pairs of dogs. Urinary FDP were then tested daily. Post-operatively FDP levels rose to an average of 80 µg/ml, falling below 20µg/ml within four days of transplantation. Predictive rises in FDP levels occurred in 11 of the 12 dogs from one to three days prior to biochemical evidence of rejection.

Very high level in a dog with renal artery thrombosis
Do not conc urine. Freeze & then centrifuge before test

E. N. Wardle, P. R. Uldall and J. Swinney

Radiofibrinogen catabolism studies have been performed in patients with renal allografts to assess their use in the evaluation of rejection. Until the third week post-operatively accelerated fibrinogen catabolism was found in all patients. Nevertheless rejection occurred in all patients at this stage and responses to heparinization show that accelerated catabolism was due to intra-renal coagulation. The effect was not due to high-dose corticoids. Even after three months of allograft survival two thirds of patients with rejection show increased fibrinogen catabolism: most of those who did not were already on anti-platelet or anti-coagulant therapy. The test is a sensitive monitor of vascular rejection, which can be used over a period of two or three weeks and which could, therefore, become a means of assessing new forms of therapy. However, results are only obtained in retrospect.

LD T 2.4
CD 7 3.1
5 3.6

Peak rejection score Side effects: headache, dizzy, unable to work
Salaman. Tried Persantan - no benefit in small series these effects deep

M. Anderson, P. Dewar, L. B. Fleming, P. M. Hacking, A. R. Morley, S. Murray, J. Swinney, R. M. R. Taylor, P. R. Uldall and E. N. Wardle

A controlled trial of the use of dipyridamole for modification of renal transplant rejection has shown no benefit either clinically, pathologically or by radiological study of the renal circulation. Concurrent evaluation of platelet function studies for assessment of the vascular phase of rejection show that measurement of platelet factors 3 and 4 release are useful.

M. Fox, C. Bransom, K. Gelsthorpe and L. Henry

Anti-lymphocytic globulin (ALG) prepared in the goat has been used as an immuno-suppressive agent in renal transplantation in only one series so far with encouraging results (Shiel *et al* 1971*). The present report is of our experience with production of goat ALG, assessment of potency and its use in human renal cadaveric transplantation in 30 patients in low dose regime over two weeks. Results are compared with a similar number of controls.

ALS was raised following repeated i.v. injections of lymphocytes obtained from human peripheral blood. The gamma protein fraction was separated, concentrated and injected daily i.v. over two weeks at a dose range of 5-7 mg. per kg. per day. Potency was tested by cytotoxic and rosette inhibition titres, and skin graft survival in the monkey in some cases. All patients were treated, in addition, with standard immuno-suppressive agents.

Titres did not rise after the third boost of antigen, and some subsequently decreased. Immuno-fluorescent studies showed no anti-glomerular basement membrane activity. The ALG could be given to patients safely intravenously and there were no serious side effects. Results with this low dose regime showed kidney survival in 50 per cent of patients over six months after transplantation with no further rejection of one year. In a similar control group without ALG, 36 per cent retained their kidney graft. There was no significant increase in mortality, which was 18 per cent overall.

* Shiel, A. G. R., *et al*. *Lancet* 2, 350, 1971.

allergic, rashes, rigors
5 Arr one yr the ALG group died 6/12 13/24 within 9/25

Howman also get more infections w ALG treated is now used only for treatment of acute rejection.

A. D. Barnes and K. Hofmann

In view of the lack of improvement in results above the 50% success rate with prednisone and azathioprine, other drugs have been used in cadaveric renal transplantation. For nearly a decade there have been claims that ALG therapy is beneficial but to date there have been no randomised trials of such material.

This paper reviews 49 patients undergoing cadaveric renal transplantation between November 1971 and July 1972 with complete follow-up to January 1974. Antithymocyte globulin in a dose of 1.0 grams daily for ten days intravenously from the day of transplant was administered. The patients were randomised between ALG with standard prednisone and azathioprine and no ALG by reference to a table of random numbers. The ALG had been shown to consistently double the mean survival time of skin allografts in rhesus monkeys.

The randomisation showed an equal sex distribution and of retransplants between the two groups. The incidence of rejection was lower in the ALG group (37%) as compared with the controls (43%) and this was most marked in the re-grafts (33% against 80%). However, the worrying finding was that the mortality in the ALG group was 42% against 17% in the controls. The extra deaths were due to uncontrollable systemic infection in the early post-operative period. There is no difference in the renal function or well being of the patients with functioning transplants. There have been no late deaths associated with infection or malignancy. The conclusion was reached that the dose of ALG plus prednisone and azathioprine used represented excessive immunosuppression.

1.0g iv. 1/2 white cells daily for 10 days.
Pred 75g for 10-20 days then reduce to 25g by 3/12
Systemic infection 8/16 control 3/30 due mainly to bacteria rather than fungi etc. Now treat of 0.5g ldy s.c. too early not bacteria trouble

E. N. Wardle

Endotoxins of gram negative organisms and Candida and staphylococcal bacteraemia can be detected by gelation of the protein content of the white cells of the horse shoe crab, Limulus polyphemus, by the patient's plasma. Extraction has been performed by the method of Reinhold and Fine and a semiquantitative assay performed.

Positive results were obtained in 65% of patients with renal transplants and infection, but not at rejection and not in patients with vascular complications. Attention is drawn to the protracted endotoxaemia and high susceptibility of transplant patients. Nevertheless, the steroids protected against Schwartzman renal damage and transplant rejection did not follow after endotoxaemia.

AGENDA FOR THE BUSINESS MEETING

to be held at 2 p.m. on Wednesday, 17th April, 1974

1. Minutes of the Annual Business Meeting held on October 17th, 1973 (see below)
2. Matters arising from the Minutes.
3. Election of New Members.
The applicants listed below have been considered and approved by the Committee.
4. Resignations: T. A. Casey, P. H. Smith.
5. Interim statement by Treasurer on the Society's Appeal to Industry.
6. Arrangements for Autumn Meeting.
7. Proposal to offer a U.K. venue for the 7th International Congress of The Transplantation Society: report from the Provisional Organising Committee.
8. Any other business.

MINUTES OF THE ANNUAL BUSINESS MEETING

Held on October 17th, 1973

R. Y. CALNE was in the Chair.

About 80 members attended.

1. The Minutes of the Business Meeting held on October 18th, 1972, were approved.
2. Dr. Heather M. Dick and Mr. R. A. Sells were elected as committee members to replace Prof. J. R. Batchelor and Mr. J. R. Salaman.
3. Thirty-two new members were duly elected; 2 resignations were noted.
4. The General Secretary reported that membership now stood at 237. The committee had met six times since the Society was formed. Dr. G. D. Snell had expressed his appreciation of his election to Honorary Membership. Members of the Society had not been exactly forthcoming with suggestions for scientific activities and were asked to send ideas for meetings to the Meetings Secretary. The General Secretary thanked the two retiring committee members, J. R. Batchelor and J. R. Salaman, for their valuable help in seeing the Society through its first year, and he expressed his and the Society's gratitude to the B.S.I., and especially Mrs. Irene Batty and Prof. J. L. Turk, for their support.
5. The Meetings Secretary reported on past and future events. Attendance at meetings had generally been very good. The fact that the January, 1974 meeting was being held in London was not to be taken as a precedent—normally the January meeting would be held in the provinces and the 1975 meeting would take place in Cardiff.
6. The Treasurer gave a written report of the Society's finances up to May 31st, 1973; they showed a slender balance which had been achieved only because of the generosity of the B.S.I. Subscriptions would probably have to go up in the not too distant future, but meanwhile the committee was proposing to make an appeal for support to industry.
7. It was reported by the General Secretary that, because of the war in the Middle East, Peltours (London) had not yet received information about travel arrangements being made for the 5th International Congress of The Transplantation Society. He had urged Peltours to include cheap accommodation, including hostel rooms, in their proposals.
8. The General Secretary reported that programmes for the 2nd International Congress were now available, and that the transplantation content of the Congress was not as great as it might have been because the Jerusalem Congress was being held soon after.
9. It was decided to seek affiliation to The Transplantation Society, on the understanding that members of the B.T.S. could then apply for corresponding membership.
10. It was agreed that the Congress Organising Committee should be reconstituted to prepare a bid for the 7th Congress of The Transplantation Society in 1978. Proposals were to be prepared in time for the next Business Meeting in April, 1974.