## BRITISH TRANSPLANTATION SOCIETY

Minutes of the business meeting of the British Transplant Society held on Wednesday, 13th July, 1977, at the Postgraduate Medical Education Centre, City Hospital, Nottingham.

In the Chair — Professor P. J. Morris.

Apologies for absence were received from Professor J. R. Batchelor and Mr. R. A. Sells.

1. **Minutes of the last business meeting.**
   The Minutes of the business meeting held on 27th April, 1977, at the Wellcome Foundation Building in London were approved and signed.
2. **Matters arising.**
   (a) **Brain Death:** The Chairman reported that the Department of Health and Social Security were to send a letter to every doctor in the United Kingdom telling them about the criteria of brain death and the relevance to transplantation. Work was proceeding with the Department of Health on drawing up a 'code of practice' which will involve all aspects of transplantation and this would have universal circulation.
   Following a report from Dr. McGeown it was felt that the Society should write to the State Pathologist in Belfast pointing out that the Home Office had already circulated all Coroners in the United Kingdom asking for their co-operation in obtaining kidneys for transplantation, and that he was not acting in accordance with the Official Home Office policy.
   (b) **Reduction of the number of B.T.S. meetings:** As the meetings of the Society were already arranged for 1978, and for the summers of 1979 and 1980, it was felt that this matter should be deferred for the time being, but that thought should be given by members to the question of whether it would be possible to accommodate the Society's meetings outside London if provincial hosts could be found.
3. **Election of new members.**
   The election of the following six applicants was agreed:

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| Bakkaloglu, Mehmet. | Van Es, L.A., | Thomas, Angus W. |
| Vaughan, Andrew T. M. | Kubo, Ralph T. | Jeekel, Hans J. |

4. **Future meetings.**
   The spring meeting of the Society would be held at the Royal Free Hospital, London on 29th March, 1978, when short papers will be read at all sessions. Abstracts to be requested early in 1978 (Mr. O. Fernando—local organiser).
   Summer meeting: Wednesday, 28th June, 1978—Newcastle.
   Autumn Meeting: Joint meeting with the British Society for Immunology.
   October 19th, 1978.
   1979—Summer meeting—Leicester.
   1980—Glasgow.
5. **Treasurer's report.**
   The Treasurer reported that the balance in hand was about £600, a great improvement on last year. He asked that anyone who had not cancelled their standing order for payment of the subscription to do so, as he felt the £2 should no longer be refunded to individual members, and that this should be considered as a donation to the central funds in future. The annual subscription for membership was to be paid in December.
6. **Higher Surgical Training.**
   The Chairman reported that he was preparing draft proposals to take to the Specialist Advisory Committee in General Surgery (Joint Committee in Urology (J.C. on H.S.T.) in October regarding higher surgical training for Transplant Surgeons. He asked for views on what members felt constituted adequate training facilities etc.
   A lengthy discussion ensued at which several important factors were raised. The meeting felt generally that to be a recognised centre involved a number of features—a reasonable number of transplants to be done per year, research facilities, immunological facilities and adequate post-operative care



# MEETING OF
# THE BRITISH TRANSPLANTATION SOCIETY

19th October, 1977

THE WELLCOME BUILDING, EUSTON ROAD, LONDON

10.00 a.m. **Symposium: "HLA and Disease—A Review of the VIIth Workshop". Part I.**

11.15 a.m. Coffee

11.45 a.m. **"HLA and Disease". Part II.**

Chairmen and Organisers:

**Professor J. R. Batchelor (East Grinstead).**
**Professor P. J. Morris (University of Oxford).**

Participants:

**Professor W. Bodmer (University of Oxford).**
**Dr. Julia Bodmer (University of Oxford).**
**Professor H. Festenstein (The London Hospital).**

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1.00 p.m. Lunch

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2.00 p.m. Annual General Meeting (Agenda attached)

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**Short papers: Chairman R. W. G. Johnson (Manchester).**

2.45 p.m. **N. W. Nisbet and James Menage (Oswestry).**
Haematopoietic Grafts in Osteopetrosis.

3.00 p.m. **A. F. Fernando, D. M. G. Armstrong, J. R. Griffiths, W. F. Hendry, E. P. N. O'Donoghue, T. Sherwood, Agnes Smith, J. P. Ward, L. E. Watkinson, H. N. Whitfield and J. E. A. Wickham. (St. Bartholomew's Hospital, Institute of Urology).**
The prevention of Renal Warm Ischaemic Injury by Inosine.

3.15 p.m. **Annette Bryan, Paula Stenning, R. A. Sells. (Liverpool).**
The Effect of Graft Passage on Murine Auxiliary Heart Graft.

3.30 p.m. **Christine M. Evans, M. T. Thompson, R. J. Blamey (Nottingham).**
An Examination of the Popliteal Node Weight Assay as a Test of Immune Competence.

3.45 p.m. Tea

4.00 p.m. **Short papers: Chairman R. Wood (Leicester).**

**C. G. Winearls, P. R. Millard, P. J. Morris (Oxford).**

The Use of Cyclophosphamide and Enhancing Serum to suppress Renal Allograft Rejection in the Rat.

4.15 p.m. **R. A. Sells, P. K. Basu, L. Brookes, D. Whitmore (Liverpool and Upjohn Limited).**

Blood Steroid Levels in Cadaver Renal Allograft Recipients.

4.30 p.m. **Valerie C. Joysey, James H. Roger, David B. Evans and Basil M. Herbertson (Cambridge).**

Differential Kidney Graft Survival Associated with Interaction between Recipient ABO Group and Pretransplant blood transfusion.

4.45 p.m. **D. M. Evans, J. W. Fabre and P. J. Morris (Oxford).**

Studies on the effect of Splenectomy and Anti-Lymphocyte Serum on the Rejection of Ranal Allografts in the Rat.

5.00 p.m. **M. S. Knapp, J. R. Cove-Smith, R. W. Blamey, M. Heath (Nottingham).**

Reciprocal Serum Creatinine Plots following Renal Transplantation.

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## FUTURE MEETINGS

The next meeting of the Society will be held on March 29th, 1978 at the Royal Free Hospital, London. The Summer Meeting will be held on Wednesday, 28th June, 1978 in Newcastle. Local organiser Mr. Ross Taylor.

Members are reminded that the subscription is now £5, and should be paid by cheque, **not** by Banker's Order. If you have already paid £3 by Banker's Order, please cancel the order immediately and send an additional cheque for £2. If you have not already paid your subscription, then please send a cheque for £5 to the Treasurer forthwith. At present £400 is outstanding in subscriptions and members are reminded of Rule 11 of the Constitution—

> "Any member whose subscription is two years in arrears and who has been duly notified of the fact shall, if the Committee sees fit, cease to be a Member of the Society. . . ."



## 1. HAEMATOPOIETIC GRAFTS IN OSTEOPETROSIS

**N. W. Nisbet and Janis Menage**

*(Oswestry)*

Osteopetrosis is a rare bone disease that occurs in man, animals and birds, is thought to be due to defective osteoclasis, and has proved to be a useful tool in osteogenic research at the cellular level. Grafts of histocompatible haematopoietic cells from bone marrow and spleen to new born osteopetrotic mice and rats leads to resolution of the defective bony absorption, while bone formation proceeds normally. This also happens in adult osteopetrotic mice parabiosed to normal partners showing that the vascular circulation contains an osteoclastic precursor cell. This tends to disprove the unitary theory of osteogenesis, that osteoblasts and osteoclasts are interchangeable and derived from the same precursor stem cell.

The extent of the repopulation of the haematopoietic system of cured animals was unknown, so we investigated this in osteopetrotic mice by using the T6 chromosome marker. We found that chimerism was minimal, in contrast to other workers who used radiation chimeras. This suggests that cell-cell interactions are involved as in other biological systems.

In man the malignant-recessive-juvenile form of the disease is always fatal. There is now a chance of alleviation by histocompatible bone marrow grafts.

## 2. THE PREVENTION OF RENAL WARM ISCHAEMIC INJURY BY INOSINE

**A. F. Fernando, D. M. G. Armstrong, J. R. Griffiths, W. F. Hendry, E. P. N. O'Donoghue, T Sherwood, Agnes Smith, J. P. Ward, L. E. Watkinson, H. N. Whitfield and J. E. A. Wickham.**

*(St. Bartholomew's Hospital and Institute of Urology)*

Though highly sophisticated techniques are available for long term renal preservation, the lack of effective means of preventing warm ischaemic injury before these techniques can be applied precludes the salvage of a number of cadaver kidneys for transplantation.

Experiments in rats and dogs have shown that inosine is highly effective in preserving renal function during an hour's warm ischaemia. This effect was far superior to that of phenoxybenzamine, chlorpromazine, allopurinol, ATP, C-AMP, adenosine, heparin or mannitol and was seen whether inosine was given intravenously, intraperitoneally or directly through the renal artery.

With one hour's ischaemia at 37°C in dogs, inosine perfused kidneys maintained significantly lower plasma creatinine values than controls and the creatinine clearance on the 7th day was the same as that in a normal dog kidney.

Current experiments show that the beneficial effect of inosine is maintained even after two hours of warm ischaemia. Furthermore, with inosine perfusion and one hour's warm ischaemia there is rapid post-ischaemic re-synthesis and restoration of renal tissue ATP levels, fine detail angiography reveals immediate perfusion of the whole renal vasculature and electron microscopy demonstrates that the renal tubular brush border is maintained intact. Urinary gamma-glutamyl-transpeptidase excretion, which is a good index of ischaemic injury, is significantly lower after inosine perfusion of the warm ischaemic kidney.

This accumulated evidence suggests that inosine is more effective than any other agent hitherto used for maintaining the integrity of the kidney during warm ischaemia.

## 3. THE EFFECT OF GRAFT PASSAGE ON MURINE AUXILIARY HEART GRAFT SURVIVAL

**Annette Bryan, Paula Stenning, R. A. Sells**

*(Liverpool)*

Murine foetal heart grafts placed beneath the ear skin of 3 month old male hosts are vascularised within two days, and undergo rejection around 8.5 days post transplant (Balb/C donors → CBA hosts). Re-transplantation of Balb/C hearts from primary CBA to secondary CBA hosts 5 days after primary grafting results in prolongation of mean survival time (MST)* to 12 days (n=16). Similarly, prolongation of graft survival is seen using $F_1$ donors:

(CBA x Balb/C) $F_1$ → CBA: MST = 11.5 days (n=14).
(CBA x Balb/C) $F_1$ → CBA → CBA: MST =, 16 days (n=14).

Possible explanations include the following:

(a) Hearts are not undergoing rejection at the time of passage and are rejected as slowly as primary grafts by the secondary hosts.
(b) During their sojourn in the primary host depletion of passenger leucocytes (PL) occurs, rendering the grafts less immunogenic.

To elucidate the mechanism of prolongation, Balb/C hearts were passaged in C 57 Bl. primary hosts and transplanted into CBA secondary recipients: the MST was 12 days (n=16). This indicates that rejection is interrupted by passage, and substitution of donor PLs by third party allogeneic PLs does not apparently alter the immunogenicity of the graft.

However, passage of Balb/C hearts through (CBA x Balb/C) $F_1$ mice prior to grafting into CBA caused accelerated rejection (MST = 7.5 days n=18). Thus heart rejection is delayed by passage, and passenger leucocyte depletion does not appear to account for this. The finding that passage through $F_1$ hosts results in accelerated rejection, could result from proliferation of donor PLs in response to host alloantigen which could render the graft more immunogenic to the secondary host.

* (MST = the interval between the time of removal of the graft from the donor and the time when 50% of the grafts cease functioning due to rejection).

## 4. AN EXAMINATION OF THE POPLITEAL NODE WEIGHT ASSAY AS A TEST OF IMMUNE COMPETENCE

**Christine M. Evans, M. T. Thompson, R. W. Blamey**

*(Nottingham)*

The hypothesis has been advanced that popliteal node weight assay in the rat may be used to determine the degree of immunocompetence of the cell donor in the assay (Salaman, et al, 1975).

It has been suggested that patients whose lymphocytes give only a small response in the assay are those best suited as allograft recipients. In an attempt to confirm this hypothesis two criteria have been examined:

1. That cells from immunosuppressed allogeneic animals should give a lesser response that cells from normal allogeneic animals.
2. That cells from animals in a stimulated immune state (rejecting a transplant) should give a greater response than cells from unstimulated animals.

This was tested in allogeneic rats. 2 x $10^6$ AS lymphocytes were injected into the left footpad of the Wistar (W) rats and the popliteal node was removed at 7 days and compared with the control right popliteal node.

| | | *W rats* |
|---|---|---|
| *Cells from* | *No.* | *Ratio popliteal node weight Test : Control* |
| Unsensitized AS | 11 | 2.8 ± 0.6 |
| Immunosuppressed AS | 9 | 1.7 ± 0.4 |
| AS rejecting skin allograft from W (specifically presensitised) | 11 | 1.7 ± 0.5 |
| AS rejecting skin allograft from Sprague-Dawley (SD) | 3 | 1.7 ± 0.2 |

Thus, although the first criterion (above) is satisfied, the second is not and this has been confirmed with lymphocytes from patients rejecting renal allografts. The hypothesis is, therefore, not fully upheld.

Salaman, J. R., Millar, D., Brown, P. (1975) Transplantation *19*, 505.



## 5. THE USE OF CYCLOPHOSPHAMIDE AND ENHANCING SERUM TO SUPPRESS RENAL ALLOGRAFT REJECTION IN THE RAT

**C. G. Winearls, P. R. Millard, P. J. Morris**

*(Oxford)*

In the strong F1 (DA x Lewis) to Lewis renal allograft model passive enhancement provides only partial suppression of rejection. Although suboptimal doses of ALS act additively in this situation, azathioprine and prednisolne do not. The effect of cyclophosphamide has been titrated in this model and suboptimal doses used with enhancing serum. Dose levels of 50% of the optimum suppress rejection completely in enhanced animals. If treatment was administered for 14 days the effect was not permanent in that all animals rejected after withdrawal of the drug. If the course was extended to 28 days permanent suppression was obtained. Cyclophosphamides did not antagonize the effect of enhancing serum despite altering the humoral response. This is in contrast to its inhibitory action on active enhancement of tumour grafts (Zola 1975).

Zola, H. (1975), Ann. Immunol. (Inst. Pasteur), 126c, 51-62.

## 6. BLOOD STEROID LEVELS IN CADAVER RENAL ALLOGRAFT RECIPIENTS

**R. A. Sells, P. K. Basu, L. Brookes, D. Whitmore**

*(Liverpool and Upjohn Ltd.)*

The relationship between blood levels and the immunosuppressive effects of steroids remains unclear. Evidence exists that kidney grafts are rejected more commonly in patients receiving anti-epileptic drugs where enzyme induction may cause low steroid blood levels. In order to find out whether graft survival correlates with blood steroid levels we have studied 19 patients with well functioning grafts (Group I) and 13 patients who had rejected their grafts (Group II). Three in group I and two in group II were receiving phenytoin and phenobarbitone at the time of grafting. After fasting, Methylprednisolone (MP) 0.5 mg/kg was given orally and serum samples were assayed for MP. Peak levels and half life values were correlated with graft outcome and complications. Mean peak levels and half life values in Group I (470.6 ng/ml ± 33.4 SE; 5.2 hours ± 0.16) were not significantly different from those values in Group II (489.7 ng/ml ± 44.3; 5.6 hours ± 0.27), both were significantly higher ($p < 0.001$) than values obtained in those five patients treated with anticonvulsants (169 ng/ml ± 16.2; 2.3 hours ± 0.5). No significant correlation could be found between serum MP levels and blood sugar, blood pressure, cushingoid changes, wound breakdown, bone changes or serum albumin at one week, one month and six months after transplantation. We conclude that the immunological and metabolic consequences of oral steroid therapy depend not so much on bioavailability of the drug as on end-organ sensitivity, which appears to vary greatly between individuals.

## 7. DIFFERENTIAL KIDNEY GRAFT SURVIVAL ASSOCIATED WITH INTERACTION BETWEEN RECIPIENT ABO GROUP AND PRETRANSPLANT BLOOD TRANSFUSION

**Valerie C. Joysey, James H. Roger, David B. Evans, and Basil M. Herbertson**

*(Cambridge)*

In 1973 we reported significantly superior survival of kidneys transplanted to blood group O recipients compared with recipients of those from blood groups A, B and AB taken together. In the present extended series the difference between these categories was less prominent and no longer significant.

In the present study, blood transfusion significantly improved the survival of kidney grafts in patients of blood group O, but not of combined A, B and AB groups. The difference between the graft protecting effect of transfusion in group O and combined groups A, B and AB recipients was also significant. This suggests that the improvement in subsequent survival after transfusion is either confined to blood group O recipients, or is much stronger in them than in recipients of other groups. Our previous policy of restriction of blood transfusion is seen as one of the causes of the reduced superiority of group O over other groups in the present extended series in comparison with our 1973 series.

It seems that transfusion of group O recipients can markedly improve the prognosis of a subsequent first kidney graft.

## 8. STUDIES ON THE EFFECT OF SPLENECTOMY AND ANTI-LYMPHOCYTE SERUM ON THE REJECTION OF RENAL ALLOGRAFTS IN THE RAT

**D. M. Evans, J. W. Fabre and P. J. Morris**

*(Oxford)*

Following reports of an immunosuppressive effect of splenectomy in renal transplantation in the rat (Fabre and Batchelor, 1975, Transplantation, *20*, 219.) further studies have been carried out in different strain combinations. The effect of splenectomy at the time of transplantation, and the interaction of splenectomy with ALS were investigated in the weak (DA X Lewis) F1 to DA and the strong DA to Lewis renal allograft models.

In the (DA X Lewis) F1 to DA combination splenectomy produced only a slight immunosuppressive effect. Dose response studies of ALS were done, and a suboptimal dose of ALS was combined with splenectomy. The combination gave virtually complete suppression of rejection, suggesting at least an additive effect between splenectomy and ALS in this strain combination.

The experiment was repeated in the strong homozygous DA to Lewis model. No effect of splenectomy was demonstrated on renal allograft survival, and little if any additive effect with a suboptimal dose of ALS found.

The clinical implications of these studies will be discussed.

## 9. RECIPROCAL SERUM CREATININE PLOTS FOLLOWING RENAL TRANSPLANTATION

**M. S. Knapp, J. R. Cove-Smith, R. W. Blamey, M. Heath**

*(Renal Unit, City Hospital, Nottingham)*

Several authors[1,2] have described the advantages of plotting the reciprocal of serum creatinine against time in patients with chronic renal failure. The linear fall in creatinine values reflects constant loss of nephron function and can be used to predict when dialysis and transplantation will be required.

We have confirmed these observations and have also applied the technique to a retrospective analysis of patients with renal transplants.

Serum creatinine was measured daily on a Technicon autoanalyser in 30 patients following renal transplantation and th results plotted on reciprocal (hyperbolic) graph paper against time in days. In addition serum creatinine values were corrected for ideal body weight to eliminate changes due to water retention or diuresis.

From the onset of graft function, whether immediate or delayed, the serum creatinine values fell in a straight line. A similar linear relationship was observed during recovery from rejection episodes. Furthermore, the falling slope of improving function or the plateau of stable function changes abruptly to a rising slope at the onset of episodes of rejection or obstruction. Whereas with serum creatinine values uncorrected for changes in body water and not displayed graphically the significance of a rise is uncertain, with the reciprocal plot even a single value deviating from the predicted straight line may herald a rejection episode. This method of presentation thus appears to allow earlier diagnosis of rejection. Finally the rate of rise of creatinine plots was similar in both "mild" and "irreversible" rejection, suggesting that loss of nephron function occurs at a similar rate.

*References*

[1] Talwalkar, Y. B. and Mandel, S. (1977) Lancet i. 366.

[2] Rutherford, W. E. et al (1977) Kidney International 2. 62.



## AGENDA FOR THE ANNUAL BUSINESS MEETING

**To be held on Wednesday, 19th October, 1977 at 2 p.m.**

1. **Minutes of Business Meeting held on Wednesday, 13th July, 1977.**
2. **Matters arising from Minutes:**
   (a) Progress of negotiations with the D.H.S.S. concerning the issue of Brain Death Criteria and Code of Practice. Secretary to report.
   (b) Future Meetings of the Society:
   As decided in October 1976, there will continue to be three meetings a year. The Committee suggests that the October meeting should be held at the Wellcome Institute in London, the Spring meeting should be held by rotation at a London Teaching Hospital, and the summer meeting should be held outside London. Meetings Secretary to report.
   (c) Higher Surgical Training in Transplantation.
   Chairman: P. J. Morris to report.
3. **Election of Officers and Committee members.**
   The Committee of the B.T.S. for 1977/78 is as follows:

| | Elected | Due to Retire |
|---|---|---|
| *Chairman: Professor J. R. Batchelor | 1974 | 1977 |
| General Secretary: R. A. Sells | 1975 | 1978 |
| Meetings Secretary: R. W. Blamey | 1976 | 1979 |
| Treasurer: Dr. M. W. Elves | 1975 | 1978 |
| Ordinary Committee Members. | | |
| *Mr. A. D. Barnes (ex officio) | 1974 | 1977 |
| Mr. D. Hamilton | 1976 | 1979 |
| Dr. Mary G. McGeown | 1975 | 1978 |
| Mr. J. R. Salaman | 1975 | 1978 |
| **Professor P. J. Morris | 1976 | 1979 |
| *Dr. E. Simpson | 1974 | 1977 |
| Dr. J. R. Sanderson (B.S.I. Representative) | | |

**not eligible for re-election.*
***Chairman-elect.*

There are thus three vacancies on the Committee for Ordinary Members. The following names have been received:

| NOMINEE | PROPOSER | SECONDER |
|---|---|---|
| J. Sachs (London) | D. Hamilton | M. W. Elves |
| B. Hulme (London) | M. McGeowan | R. A. Sells |
| V. Joysey (Cambridge) | R. J. Batchelor | R. W. Blamey |
| J. Castro (London) | G. Williams | G. D. Chisholm |

Ballot forms for this Committee are attached; please bring the form with you to the meeting, or if you are unable to attend send it to the General Secretary.

4. **General Secretary's Report.**
5. **Treasurer's Report.**
6. **Future Meetings. Meetings Secretary to Report.**
7. **Travel Arrangements for members to go to the Transplantation Society meeting in Rome, 1978.**
   Several quotations for group travel arrangements have been received by the Committee. The most competitive and suitable of these will be put forward to the membership.
8. **Transplantation Society meeting 1982.**
   An Action Committee has been created to put forward proposals to the Transplantation Society for their 1982 meeting to be held in England. The Chairman will report.
9. **Election of members:**
   The following applications have been approved by the Committee.
   Kuppner, Maria Christina, B.Sc. Thompson, Michael. Knapp, Martin S., M.D., F.R.C.P., Pawelec, Graham Peter, M.A. (Cantab). Bakkaloglu, Aysin, M.D., Burrows, Lewis, M.D., F.A.C.S., Pierpaoli, Walter, Med.D., Ph.D.
10. **Any other business.**