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Abstracts

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Quantitation of the intrarenal uptake of immune–complexes by macrophages in diffuse proliferative glomerulonephritis. *N.W. Boyce, S.R. Holdsworth, Monash University Department of Medicine, Prince Henry's Hospital, St. Kilda Road, Melbourne, 3004 Victoria, Australia.* The intrarenal processing of circulating immune–complex–like material (CIC's) is traditionally attributed to resident glomerular mesangial cells. To assess the contribution of infiltrating mononuclear cells to CIC processing by diseased glomeruli, we have utilized an isolated perfused kidney system (IPK) to quantitate the specific glomerular uptake of CIC's [as μg of aggregated IgG per 10^4 glomeruli ($\mu g/10^4$glom)]. The IPK allows the study of direct uptake of complexes by the kidney itself, and the effects of functional blockade of mononuclear phagocytosis on the renal uptake of complexes. This preparation is devoid of influences from other components of the reticuloendothelial system and allows effective control over renal haemodynamics, thus ensuring uniform delivery of immune–complexes to the kidney in normal, macrophage–infiltrated and anti-macrophage serum–treated preparations. Mononuclear cell infiltrated glomeruli from animals with diffuse proliferative glomerulonephritis had a significantly augmented uptake of CIC's (48.9 ± 3.8 $\mu g/10^4$gloms : normal 11.8 ± 0.6 $\mu g/10^4$glom : $P < 0.01$). Specific blockade of mononuclear cell function by perfusion with anti-macrophage serum prevented increased CIC uptake (12.8 ± 1.2 $\mu g/10^4$gloms : $P < 0.01$), but had no effect on the CIC uptake of normal kidneys (13.1 ± 1.2 $\mu g/10^4$gloms). Thus, in diffuse proliferative glomerulonephritis the observed increase in the glomerular clearance of CIC's was due to phagocytosis by mononuclear cells. This study indicates that infiltrating, bone marrow–derived mononuclear cells may significantly contribute to the glomerular handling of circulating immune aggregates by nephritic glomeruli.

Monoclonal antibodies (McAbs) to non-glomerular basement membrane (GBM) glomerular capillary wall (GCW) antigens in the rat. *M.J. Nicol, J.H. Miller, T.J. Neale, Department of Physiology, Victoria University of Wellington and Wellington Clinical School of Medicine, New Zealand.* The role of fixed GCW antigens of non-GBM origin in the immunopathogenesis of glomerulonephritis (GN) is a current subject of intense research interest. Evidence has emerged which suggests that in some experimental animal models of GN, discretely represented native GCW antigens may directly bind antibody, not only producing a granular pattern of immunofluorescence (IF) that in the past has been equated with circulating immune complex deposition, but also functional injury as expressed by proteinuria. We sought to define such GCW antigens in Lewis rat glomeruli using McAb produced against GBM-depleted glomerular plasma membranes (GMF). Balb/C mice were immunised intrasplenically or intraperitoneally with GMF and their splenocytes fused with NSI myeloma cells. Culture supernatants from resulting hybridomas were screened for McAb reacting with GCW antigens by micro-ELISA, using GMF as antigen, and by indirect IF microscopy on normal Lewis rat kidney. From four fusion experiments 17 positive hybridoma clones have been isolated, all producing a granular IF pattern of glomerular binding in vitro. To date three McAbs have been examined in vivo; two bind to glomeruli producing granular IF patterns at one hour. An 8M urea extract of rat glomeruli run on SDS-PAGE was examined by Western immunoblotting using SC5, an IgM McAb, as a probe. Reactivity was predominantly with protein bands corresponding to 53, 120 and 175 kd. Intravenous injection of 10 mg of SC5 to normal Lewis rats produced an increase in urine protein excretion. This study demonstrates that McAb can be produced which define single discontinuously represented non-GBM, GCW antigens in the rat.

Expression of macrophage differentiation antigens on human mesangial cells. *R. Andreesen, R.C. Atkins, Department of Nephrology, Prince Henry's Hospital, Melbourne, Australia.* It is believed that only a few mesangial cells (3 to 5%) are bone marrow–derived and belong to the heterogenous group of resident tissue macrophages (MO) the remainder being of smooth muscle origin. In an attempt to further define the origin and heterogeneity of mesangial cells, we have used monoclonal antibodies (mAbs) against MO membrane antigens specific to maturation stages beyond the blood monocyte (mo) level. MAX.1 and MAX.11 mAbs were developed by immunizing mice with mo-derived MO grown on hydrophobic teflon foils and shown to be MO lineage restricted. PLP fixed cryostat sections of normal human kidney were tested for reactivity with MAX mAbs using a sensitive four–layer–immunoperoxidase method. Commonly used mAbs to identify mo-MO (common leukocyte, Ia-like, FMC32) were also employed. In normal mesangium no Ia^+ $FMC32^+$ cells could be detected. However, a strong expression of MAX.1 and MAX.11 was seen on all mesangial cells, but not endothelial or epithelial cells in the glomerulus. These antigens were also expressed on smooth muscle cells of the afferent arterioles, but not on other blood vessels in medulla and cortex nor in any other tissue type studied (spleen, lymphnode, liver). As the MAX antigens are restricted to site–specific MO, mainly of the exudate type in body fluids but not expressed on Kupffer cells, microglia, granuloma cells, and free and fixed MO in lymphnode and spleen, their detection on mesangial cells and afferent arterioles is of great interest. Mesangial cells and mature MO share several functions such as secretion of IL-1 and lipoxygenase products as well as phagocytosis. As both mesangial cells and mo-derived MO exhibit these otherwise very restricted membrane antigens, it is tempting to speculate that perhaps the entire mesangial cell population, although devoid of any conventional MO membrane antigens, belongs to the heterogenous family of end–stage matured MO.

Evidence for hydroxyl radical mediation of immune renal injury: Abrogration of renal injury and neutrophil hydroxyl radical generation by desferrioxamine. *N.W. Boyce, S.R. Holdsworth, Monash University Department of Medicine Prince Henry's Hospital, Melbourne 3004, Australia.* The acute phase of glomerular injury in a model of antiglomerular basement–membrane antibody–induced glomerulonephritis (antiGBM-GN) in rabbits was shown to be neutrophil–dependent using nitrogen mustard depletion studies. Administration of desferrioxamine (DFX) prevented the development of proteinuria in this model of renal injury [24 hr protein excretion (mean SEM): – antiGBM-GN/DFX = 16.2 ± 2.9 mg cf. antiGBM-GN control = 271.5 ± 92.2 mg : $P < 0.01$]. Antibody binding levels, glomerular filtration rates, circulating complement, neutrophil counts and glomerular C3 deposition, and neutrophil infiltration did not differ between DFX treated and antiGBM-GN groups. In vitro assay systems to assess oxygen radical production [superoxide anion (O_2^-) and hydroxyl radical ($OH \cdot$)] by neutrophils activated via the interaction of antiGBM antibody, GBM and complement were established. In these assays DFX inhibited $OH \cdot$ production by immunologically–stimulated neutrophils (ISN) [nM

diphenol/hr/10^6 cells, mean ± SEM, ISN/DFX = 8 ± 2 cf, ISN = 191 ± 22 : $P < 0.01$], while production of O_2^- was uneffected [nMO_2^-/hr/10^6 cells, mean ± SEM, ISN/DFX = 29.1 ± 4.3 cf, ISN = 32.6 ± 2.5 : $P > 0.05$]. These studies demonstrate that the iron chelator, desferrioxamine, can prevent neutrophil–dependent immune renal injury by interfering with neutrophil function. Together, the in vivo and in vitro data strongly suggest that neutrophil–dependent immunological renal injury is mediated via hydroxyl radical production by activated neutrophils within glomeruli.

A comparison of the kinetics of circulating and splenic auto-anti-idiotypic antibodies after $HgCl_2$ in the BN rat. *J.A. Savige, C.M. Lockwood, MRC Clinical Immunology Unit, Royal Post-graduate Medical School, London, United Kingdom.* The administration of the polyclonal activator $HgCl_2$ (1 mg/kg i.p.) to Brown Norway (BN) rats on days 0, 2, 4 and 7 resulted in the cyclical development of both direct (IgM) splenic plaque forming cells (PFC) specific for glomerular basement membrane (GBM) (peaks at days 9 and 23) and circulating anti-GBM antibodies (peaks at days 11 and 23–25). Anti-idiotypic antibodies to anti-GBM antibodies were sought in the serum of four BN rats using the glomerular eluate obtained from diseased rats. Eluted antibody was radiolabelled (2.5×10^6 cpm ^{125}I. mcg^{-1}), pepsin–digested and the resulting *F $(ab)_2$ fragment used as a probe in a precipitation assay with 4% PEG. Two peaks of serum auto-anti-idiotypic activity were noted: at day 11 (14,405 ± 4221 cpm bound M ± SD, cf 8375 ± 536 at day 0; $P < 0.01$) and at days 21 to 25 (9715 ± 1407 cpm; P = NS). Functional splenic auto-anti-idiotypic antibodies were demonstrated by an increased number of PFC, when low concentration of GBM were added to the plaquing mixture ("augmentation"), presumably as a result of the displacement of anti-idiotypic antibodies from the surface of the spleen cell, and reversal of inhibition of anti-GBM secretion. Augmentation was noted in 14 of 18 spleens during days 9 to 11; 21 of 22 between days 12 and 22, and 10 of 16 during days 23 to 26. We conclude that circulating auto-anti-idiotypic antibodies in a polyclonally–activated system demonstrate similar kinetics to corresponding idiotypic antibody. The reciprocity demonstrated between the presence of specific PFC and augmentation suggest that anti-idiotypic antibodies may have a role in the mechanisms of cycling.

Mechanisms of fibrin deposition in anti-glomerular basement membrane antibody induced glomerulonephritis in rabbits. *P.G. Tipping, S.R. Holdsworth, Monash Department of Medicine, Prince Henry's Hospital, St. Kilda Road, Melbourne, Victoria, 3004, Australia.* Fibrin is an important mediator of glomerular injury in anti-glomerular basement membrane antibody–induced glomerulonephritis (anti-GBM GN). The mechanisms involved in the initiation of fibrin deposition are unknown. The involvement of the intrinsic and extrinsic coagulation pathways was studied in rabbits developing anti-GBM GN. Glomerular injury (proteinuria, plasma creatinine, and glomerular crescent formation) was assessed in groups of six or eight rabbits on days 4, 6, 8 and 10 after the initiation of the disease and in a group of normal rabbits. All parameters increased progressively over this time as a crescentic GN developed. Glomerular fibrin deposition was assessed by immunofluorescence and ^{125}I fibrinogen deposition, and glomerular macrophage ingress by glomerular cell culture. Glomerular macrophage ingress (maximal on day six) clearly preceded the onset of fibrin deposition. Nephritic glomeruli contained augmented amounts of procoagulant activity (PCA), which activates the extrinsic coagulation pathway. Highest levels of PCA were found on day six, coincident with the maximal macrophage presence. Glomerular PCA subsequently declined as the numbers of glomerular macrophages declined. Glomerular deposition of Factor VIII related antigen, a marker of intrinsic pathway activation, was assessed by immunofluorescence and found to be present in Bowman's space only in the late stages of this disease. These observations suggest a role for extrinsic pathway activation, via PCA, in the initial stages of glomerular fibrin deposition in anti-GBM GN. Glomerular macrophages are the most likely source of this PCA. Intrinsic pathway activation may be involved in fibrin deposition in Bowman's space in the later stages of the disease.

Decomplementation studies in anti-tubular basement membrane (TBM) antibody associated tubulointerstitial nephritis (TIN). *K.M. Bannister, C.B. Wilson, Research Institute of Scripps Clinic, La Jolla, California, USA.* A role for complement in the development of anti-TBM antibody associated TIN in the rat has been suggested by the finding of *(1)* linear circumferential C3 along TBM of tubules involved in TIN and *(2)* a polymorphonuclear leukocyte influx early in the disease. This study examined the functional role of complement as a mediator in the development of TIN resulting from passive transfer of anti-TBM antibody to normal Brown–Norway (BN) rats. Lewis (LEW) rats immunized with BN renal basement membrane and adjuvants develop high titer circulating antibody reactive with BN, but not LEW TBM (radioimmunoassay (RIA) and immunofluorescence). This allo-antibody was capable of transferring histological lesions of TIN within 24 hours when as little as 3 ml of pooled sera was injected i.v. into BN recipients. Eleven BN rats received 7 ml i.v. of such LEW immune sera in two divided doses on day 0. Six of these rats were injected i.p. with purified cobra venom factor (CVF) (300U/kg) on days −1 to 5 (sacrifice). Serum C3 levels were estimated on days 0, 2 and 5 by immunodiffusion in gel. TIN (area involved) was scored by single blind examination of ten step kidney sections from each rat. C3 depletion with CVF resulted in a greater than 80% reduction in area of destructive TIN lesions and a marked decrease in total numbers of associated multinucleate giant cells. (CVF group 21 vs. controls 293) This finding was not due to differences in antibody bound as the quantity of IgG eluted from the kidneys of CVF treated rats was not significantly different from that from the control animals. Complement therefore plays an important functional role in this new model of anti-TBM antibody associated TIN.

Australian multicenter trial of cyclosporine A in renal transplantation: Preliminary report. *B. Hall, Australian Multicenter Study Group.* Cyclosporine A (CSA) therapy alone has been compared to prednisone, azathioprine and antilymphocyte globulin (ALG), and CSA for three months followed by azathioprine and prednisone (CSAZA) in a prospective randomized trial. The aim of the study was to test the effectiveness of the two CSA arms in preventing first cadaver graft rejection and to compare the morbidity and mortality associated with these arms with conventional therapy. Long term morbidity, especially relating to skin cancer, was also to be examined. CSA was commended as a 5 mg/kg i.v. bolus and then 4 mg/kg i.v. daily until oral CSA was tolerated at 12 mg/kg, reducing to 7.5 mg/kg at nine weeks. Short term CSA was given in the same fashion for 100 days; if there had been no clinical rejection for 28 days and if a renal biopsy showed no rejection, the patient was changed to AZA. After 24 months there was no significant difference in graft survival. Acute rejection was the main cause of graft loss in all groups.

	AZA	CSA	CSAZA
Patient survival at 12 months	90.1%	97.3%	94.5%
Graft survival at 12 months	76.5%	81.9%	83.9%
Total patients entered	109	100	108
Total at 12 months	57	60	55

There was a significantly higher mortality in the AZA group, compared with both CSA groups, $P = 0.027$. The most common cause of death was vascular disease in older patients (>55 years). Infection was more common in the AZA group. The only death from malignancy occurred in the AZA group, adenocarcinoma, primary unknown. There were no lymphomas. Two deaths from encephalopathy and coma occurred in the CSA group due to an unknown cause. No grafts were lost in the change from CSA to AZA. In 61 patients on CSAZA there were only four graft losses, three with established rejection and one following a renal biopsy, which showed no rejection. Six patients on CSA had prolonged oliguria > 38 days and all had reversal of renal failure on withdrawal of CSA. Seven patients on AZA changed to CSA, two because of uncontrolled rejection and five because of bone marrow suppression. Only one subsequently lost their graft from rejection. One patient continued on CSA and AZA. Serum creatinine at two months were 250 ± 150 μmol/liter in CSA; 225 ± 135 in CSAZA and 201 ± 162 in AZA. At 12 months those levels were 195 ± 95, 140 ± 64, and 169 ± 106, respectively. In this interim report it is not possible to demonstrate a difference in long–term outcome between any of the treatments used.

De novo thrombotic microangiopathy (TMA): Occurrence and differential diagnosis in three transplant patients. *J.P. Dowling, A.F. d'Apice,*

P.S. Kincaid-Smith, Departments of Anatomical Pathology and Nephrology, The Royal Melbourne Hospital, Melbourne, Australia. TMA, which has previously been reported as a de novo or recurrent insult in renal transplants, developed in three renal allograft patients and was associated with significant impairment of graft function. Patient 1, a 26-year–old female developed clinical and histological evidence of rejection four days after receiving her third allograft; immunosuppression consisted of cyclosporine A (Cy A), azathioprine and low dose prednisolone. Glomerular microthrombosis was noted on her fourth post-transplant biopsy, which also showed rejection–related glomerulopathy. Patient 2, a 22-year–old female had an acute febrile episode with graft tenderness two days post-graft. Immunosuppression was with Cy A, azathioprine and low dose prednisolone. Hemoglobin and platelets fell during the episode and biopsy showed florid glomerular and arteriolar TMA; recovery of function followed cessation of Cy A and the administration of subsequent plasmapheresis and heparinization. Patient 3, a male, 59-year–old who had been transplanted six years previously, developed acute renal failure following renal angiography for peripheral vascular disease. Immunosuppression was with azathioprine and prednisolone. Renal failure recovered incompletely with heparin and plasmapheresis and a repeat biopsy showed evidence of continuing, but mild TMA. Patients 1 and 2 may have developed TMA as a complication of Cy A therapy, with patient 1 having biopsy evidence of interstitial scarring of Cy A toxicity type and patient 2 showing no inflammatory change on biopsy to indicate hyperacute rejection. Patient 3, who did not receive Cy A, had a very strong temporal relation of TMA development to the use of radiocontrast dye, a very unusual cause of such a reaction. It is suggested that, as in the non-transplant patient with TMA, causes other than severe or hyperacute rejection such as drugs, chemical substances, viral or bacterial infection should be sought in transplant recipients.

Improvement of early renal allograft function with verapamil. *K.A. Duggan, G.J. Macdonald, J.A. Charlesworth, B.A. Pussell, Prince Henry Hospital, Sydney, Australia.* Verapamil has been shown to prevent acute renal failure in animal models if administered prior to the insult, and it may, therefore, have a role in the preservation of cadaveric renal tissue for transplantation. To investigate its usefulness in this situation, 20 renal donors were randomly allocated to treatment or control groups. Both groups received a standard preparation for nephrectomy: (i) rehydration with 0.9% saline; (ii) 1 g methyl prednisolone and 20 g mannitol intravenously one hour pre-nephrectomy; (iii) 10,000 units of sodium heparin and 100 mg phenoxybenzamine immediately before ceasing ventilation. In addition, the treatment group received 20 mg verapamil (Isoptin, Knoll Pharmaceuticals) intravenously at this point. The kidneys were perfused in situ with Ross' Solution, resected en bloc and then maintained on a Waters' oxygenator MOX100C perfusion machine until tissue matching and allocation were performed. Post-transplant management was according to the recipient hospitals' usual protocols. Early graft function was assessed by serum creatinine and urine output on days one and seven post-transplant, and by the need for dialysis in the first post-transplant week. Results for the two groups were compared by analysis of variance as determined by the F distribution. The urine outputs for the treated group were significantly greater than for controls (2208 ± 635 ml compared with 1168 ± 237 ml, $P < 0.01$) on day one and the serum creatinine concentrations were lower (0.74 ± 0.05 and 0.82 ± 0.08, respectively, $P < 0.05$). This difference was not maintained at day seven, nor was it reflected in the need for dialysis during the first post-transplant week with 13 patients in each group requiring dialysis. It is concluded, therefore, that verapamil has a role in renal allograft preservation but that its optimal dosage and route of administration have yet to be determined.

Renal autotransplantation for severe loin pain hematuria syndrome. *A.G.R. Sheil, L.S. Ibels, M.A.B. Thomas, J.C. Graham, Department of Surgery, University of Sydney and Renal Unit, Royal North Shore Hospital, Sydney, Australia.* The Loin Pain Hematuria syndrome describes the association of recurrent renal pain, hematuria and abnormalities of the intrarenal vasculature. In some patients loin pain is incapacitating. In such patients most forms of therapy have proved unsuccessful, though nerve block procedures and the operation of renal denervation have sometimes provided temporary relief. We report here three patients with this syndrome who had unremitting severe pain. In two the loin pain was unilateral and predominantly so in the third. All were narcotic–dependent for relief of pain and required repeated or persistent hospitalization. In all three patients renal function, excretion urography, and angiography were normal and renal biopsies revealed deposition of the third component of complement in renal arterioles. All were treated by renal autotransplantation, the symptomatic or more symptomatic kidneys being completely excised and reimplanted in the ipsilateral iliac fossa. Post-operative excretion urography was normal for the transplanted kidneys. Follow–up was 11 to 14 (mean 13) months. So far, all patients have had complete relief of pain from the involved kidney despite recurrence of hematuria. It is suggested that the pain of the syndrome is mediated through the autonomic system and that complete nerve section accompanying renal autotransplantation explains relief of pain. It is considered that reinnvervation is unlikely. It is too early to determine if this major procedure is justified for treatment of selected patients with incapacitating renal pain due to the Loin Pain Hematuria syndrome, but the early results are encouraging.

Hyperparathyroidism following renal transplantation. *J.K. Dawborn, W.F. Heale, L. Kotler, P.J. Miach, F. McInnes, Austin Hospital, Heidelberg, Victoria, Australia.* Six patients were identified five to ten years after renal transplantation with marked hypercalcemia (2.83 ± 0.09 mmol/liter) and raised PTH 1-84 (33 ± 8.2 (SD) pmol/liter; $N = 10$ ± 2). All had hyperparathyroidism (HPT) prior to transplantation (alk phos 510 ± 194 IU/liter) and had not been treated. Alk phos was normal in all patients after two years but PTH levels remained elevated. Hypercalcemia and hypophosphatemia developed between six to 12 months post-transplant. Three patients underwent parathyroidectomy (total wt > 3 g). Hypercalcemia and HPT were corrected by day three. All patients were normocalcemic after one week and required no medication. Biochemical parameters were compared with 43 patients transplanted for > 1 year with a creatinine clearance > 1 ml/sec. Five patients had moderate hypercalcemia and HPT two to four years after transplantation (calcium 2.68 ± 0.04; PTH 15.3 ± 1.5). 38 patients were normocalcemic. Thus persistent HPT was seen in 11 out of 49 patients; of 20 patients transplanted for less than five years, six had hyperparathyroidism. In most patients PTH returns to normal within 12 months of transplantation. The reason for failure of involution in these patients is not clear. The appearance of hypercalcemia 12 months after transplant may coincide with reduction in prednisolone, the resolution of PTH resistance or repletion of bone calcium. After 12 months the chance of resolution of HPT is small. These patients are exposed to the same risks avs patients with 1° HPT and should be evaluated in a similar way with regard to parathyroid surgery.

Pregnancy in renal transplant recipients. *J. McDowell, J. Horvath, A. Korda, D. Tiller, B. Hall, G. Duggin, J. Johnson, J. Solomon, R. Sheil, J. May, Departments of Renal Medicine and Obstetrics and Gynecology, Royal Prince Alfred Hospital, Camperdown NSW, Australia.* The abnormal reproductive function of women with renal insufficiency on hemodialysis is reversed by a good functioning graft. It has been reported that return of menstrual function and ovulation is best correlated with the level of renal function post-transplant. Since 1967 there have been 714 transplants, of whom 193 were women in the reproductive age. Nine women who had been transplanted for seven to 103 months had 15 pregnancies. All patients were on prednisone and azathioprine. The patients were aged 20 to 35 years and the serum creatinine was 70 to 573 μmol/liter when pregnancy was diagnosed. There was no recent documented rejection. Six of the nine patients had controlled hypertension. Proteinuria was present in 10 of 15 pregnancies. There was one therapeutic abortion on social grounds and the remaining 14 pregnancies resulted in one stillbirth and 14 viable infants (one set of twins). The stillbirth occurred in the only patient with a creatinine in excess of 140 μmol/liter (573 μmol/liter) and the patient subsequently returned to dialysis. In the remaining patients there was either no change or a decrease in serum creatinine during pregnancy, no episode of rejection, and no ureteric obstruction during pregnancy. Complications attributable to pregnancy were urinary tract infections in five pregnancies. Of the 14 live born infants, all were above the 10th percentile for birth weight adjusted for gestation. One infant developed meningitis at day eight and subsequently had severe mental retardation, but the remaining 13 infants showed no abnormalities and have had normal development. Pregnancy following cadaveric transplantation

remains unusual, but women with good renal function who conceive have a good chance of a relatively uncomplicated pregnancy and a normal neonatal outcome.

Correlation of clinico-pathological parameters with outcome using multiple regression analysis in lupus nephritis. *B. Leaker, P. Kincaid-Smith, Department of Nephrology, The Royal Melbourne Hospital, Parkville, 3050 Victoria, Australia.* Previous authors have attempted to predict outcome using clinico-pathological parameters recorded at initial renal biopsy using multiple regression analysis. The lack of prognostic information provided by histological data has led to the value of renal biopsy being questioned. This study has examined the power of data obtained serially to predict outcome using the above analysis. The clinical and histological parameters tested at biopsy and correlated with outcome were age, sex, serum creatinine, activity score, crescentic lesions, chronicity score, and interstitial sclerosis. At first biopsy ($N = 97$) there were significant correlations with activity, $R^2 = 9.6$, $P < 0.001$, and crescents $R^2 = 13$, $P < 0.01$. At second biopsy ($N = 63$), median time 11 months, only serum creatinine correlated with outcome $R^2 = 11$, $P < 0.05$. At subsequent biopsies ($N = 55$), median 36 months, interstitial sclerosis $R^2 = 23$ $P < 0.001$ and activity $R^2 = 32$, $P < 0.001$ correlated with outcome. A model of "best fit" to test the above parameters as predictors of outcome was derived. Activity and crescents $R^2 = 13$, $P < 0.01$, on first biopsy, serum creatinine and chronicity score $R^2 = 75$, $P < 0.05$, on second biopsy, activity and chronicity scores $R^2 = 13$, $P < 0.05$, on subsequent biopsies were the most significant predictors of outcome. The above results confirm convictions that both clinical and pathological data are able to predict outcome, albeit weakly. Histological parameters in this study were more powerful predictors of outcome than clinical data alone. Predictive models of outcome based on data obtained at a single entry point should be interpreted with caution in a variable and unpredictable disease.

Does paracetamol cause renal papillary necrosis or cancer of the kidney or urinary tract? *M. McCredie, J.H. Stewart, Renal Unit, Department of Medicine, Westmead Hospital, Sydney, Australia.* The risk of developing disease conferred by consumption of either phenacetin or paracetamol (at least 1 kg) was calculated from data acquired by questionnaire from patients with renal papillary necrosis (RPN; 80 f, 11 m), cancer of the kidney (CaK; 131 f, 229 m), renal pelvis (CaP; 82 f, 58 m), ureter (CaU; 16 f, 39 m) or bladder (CaB; 162 f) and age-matched controls taken from a random sample of the population (734 f, 652 m). The data were stratified by sex, consumption of the other analgesic and, for the cancers, smoking. Each analysis was adjusted for the effect of these factors. The risk of RPN was increased seventyfold by consumption of phenacetin, but no increased risk was conferred by paracetamol when exposure to phenacetin was controlled. Phenacetin also increased the risk of CaK, CaP and CaB but not for CaU. By contrast, paracetamol did not significantly increase the risk ratio for any of these cancers. Mantel-Haenszel risk ratios (95% confidence limits) for:

	RPN	CaK	CaP	CaU	CaB
Phenacetin	70 (50–134)	2.0 (1.3–3.0)	7.2 (4.7–11.0)	1.1 (0.4–3.0)	2.0 (1.1–3.5)
Paracetamol	0.1 (0–0.3)	1.0 (0.6–1.6)	1.1 (0.7–2.0)	1.8 (0.8–4.4)	0.7 (0.4–1.3)

While the etiological relationship of phenacetin to RPN, CaP and CaB (but not CaU) is confirmed, and that to CaK is once again suggested by these data, paracetamol cannot be implicated in the pathogenesis of either RPN or any of the cancers examined here.

Rapid improvement in lupus glomerular lesions following intensive plasma exchange. *B. Leaker, G.J. Becker, J.P. Dowling, P.S. Kincaid-Smith, Department of Nephrology, The Royal Melbourne Hospital, Parkville, 3050, Victoria, Australia.* Few authors have examined the effect of PE in severe lupus nephritis and there have been no previous reports of the effect of PE in renal histology. We report our experience of intensive PE in the treatment of 12 females with severe diffuse proliferative lupus nephritis. All had active disease with crescentic lesions demonstrated on biopsy immediately before PE. Twelve patients (median age 21 yrs) received PE for a period between six weeks and three months and were followed for a period of one to 84 months (median 24) after cessation of PE. Nine patients were also treated with high dose steroids, three patients with low-dose steroids and most patients also received cytotoxic therapy. There were no complications attributable to PE. Two patients in the high dose group died; one patient who was non-compliant progressed to ESRF; one patient suffered a MI and died in left ventricular failure. Renal function was improved in five patients and remained normal before and after PE in five patients. One patient was stable for 12 months, but returned in ESRF after two years loss from follow-up. Eight of the 12 patients were biopsied immediately after a course of PE. All but one patient (low steroid group) showed considerable dimunition of histologic activity with resolution of crescentic lesions. PE may accelerate such resolution over conventional therapy, prevent subsequent sclerosis, and preserve functional renal tissue.

Triamterene induced cylinduria and crystalluria: An animal model. *B. Leaker, K.T. Woo, D. Birch, K. Fairley, Department of Nephrology, The Royal Melbourne Hospital, Parkville, 3050, Victoria, Australia.* Renal failure, interstitial nephritis, renal calculi, and the development of distinctive urinary casts have been reported following triamterene therapy. We present an animal model of triamterene induced cylinduria and crystalluria. Twelve female rats (Hooded-Evans strain, mean wt 190 g) were randomly allocated to treatment ($N = 6$) or control group ($N = 6$). Rats were gavage fed twice daily for five days with 1 ml triamterene suspension (5 mg/ml triamterene, 200 mg/ml ascorbic acid with 200 mg/ml compound traganath suspension in distilled water) or with 1 ml control suspension. On the fourth day a 12 hour urine collection was obtained. On the fifth day rats were sacrificed. Renal tissue was mounted in OTC compound and snap frozen in liquid nitrogen. Frozen sections and unspun urine were examined under phase contrast microscopy and polarized light. All triamterene treated rats demonstrated crystals and casts in unspun urine. The casts were of waxy yellow appearance and highly refractile under polarized light. No such casts were seen in control specimens. Casts were visible to the naked eye as yellow streaks in the papilla on freshly sectioned kidney. Examination of frozen sections revealed abundant cast deposition in the large collecting ducts and papillae of all triamterene treated rats. The casts were similarly highly refractile under polarized light. No casts were seen in cortical or outer medulla areas. No casts were seen in control animals. We suggest that such cast formation may cause urinary obstruction and lead to renal failure. As triamterene is the most widely prescribed diuretic in the USA, these findings are of potential significance.

Sexual acquisition of a urinary tract infection in a man. *R.R. Bailey, B.A. Peddie, C.P. Swainson, D. Kirkpatrick, Department of Nephrology, Christchurch Hospital, Christchurch, New Zealand.* Sexual intercourse is an important risk factor for acute cystitis in women. This association is reflected in the popular term 'honeymoon cystitis'. Intercourse probably predisposes women to urinary tract infection by facilitating the entry of organisms from the urethra into the bladder, rather than by their veneral transmission. A 37-year-old man was admitted with a 24 hour history of frequency, dysuria and hematuria, and subsequently developed acute pyelonephritis. The urine contained $>10^9$ WBC and RBC/liter and was infected with Escherichia coli. He had a normal urinary tract and renal function. He recovered rapidly with trimethoprim therapy. Follow-up urine cultures were sterile. Three days before his symptoms developed, his wife presented with a seven day history of frequency and dysuria and the more recent onset of hematuria and suprapubic pain. Her urine was infected with E coli and was eradicated with trimethoprim. Before the wife developed her symptoms, the couple were having vaginal intercourse nightly and this continued for the first three days of her symptoms. The E coli isolates from both patients had the same biotype (using the API 20 E system for identification of enterobacteriaceae), an identical antibiogram when tested against 10 antimicrobial agents and the same serotype (02.H4). The temporal sequence of events and the bacteriological data argue strongly for the sexual transmission of this organism from the wife to her husband.

Contributions of indoxyl sulfate (IS), Hippurate (HIP) and o-OH Hippurate (oHH) to impaired ligand binding by uremic plasma. *P.F.*

Gulyassy, E. Jarrard, L. Stanfel, Nephrology Division, University of California, Davis, California, U.S.A. Several aromatic acids which may accumulate to high levels have been implicated as the cause of the impaired binding of drugs and endogenous ligands by uremic plasma. We have developed reliable HPLC methods to measure plasma IS, HIP, and oHH, correlated levels of each acid in plasma of 18 azotemic patients with binding of a model probe, 14 C-salicylate (SAL), and attempted to induce the binding defect in normal plasma by addition of IS and HIP. Ranges of creatinine (CR), IS and HIP were 292 to 3801, 22 to 240, and 27 to 897 μmol/liter. The oOH level was undetectable (N = 12) or low (<70, N = 3) except when SAL level was also elevated (N = 3). 14 C-SAL binding was negatively correlated with plasma CR, IS, and HIP, but the depression in uremic plasma was far larger than that of normal plasma, diluted to equal albumin concentration and spiked to azotemic levels of IS or HIP. To evaluate the additive effect of IS and HIP, 14 C-SAL binding was compared for nine pairs of uremic plasma:normal plasma spiked with both IS and HIP to the level of the azotemic plasma. 14 C-SAL binding in the spiked normal plasma was only slightly reduced (compared to normal, unspiked plasma) by 3.2 ± SD 1.1%. The 14 C-SAL binding by azotemic plasma was 17.9 ± SD 7.6% below the control binding. *Conclusion:* the ligands causing most of the impaired ligand binding in uremic plasma remain to be identified.

Renal disease in diabetics: Place of renal biopsy. *K.L. Lynn, T.J. Frendin, R.R. Bailey, C.P. Swainson, R.J. Walker, Department of Nephrology, Christchurch Hospital, Christchurch, New Zealand.* The place of renal biopsy in diabetics with clinical renal disease is unclear. From August 1974 to January 1985, 53 diabetics (26 men; 7 Maoris), aged 45 (SD 15) years, had a renal biopsy and were followed. The known duration of diabetes was 12 (SD 9) years; 39 patients had retinopathy, 33 used insulin (IDDM) and 44 were hypertensive. Indications for biopsy were: nephrotic syndrome (24), proteinuria (23), renal insufficiency (5) (2 ARF), and hematuria (1). Plasma creatinine was 0.22 (SD 0.18) mmol/liter and protein excretion (ARF excluded) 3.4 (SD2.5) g/24 hr. Diabetic nephropathy (DN) was demonstrated in 39 patients, but in 14 (6 without proteinuria) the findings were: not diagnostic (6), glomerulonephritis (GN) (4), acute pyelonephritis (1), papillary necrosis (1). Retinopathy (35 of 39 vs. 4 of 14; $P < 0.001$), IDDM (29 of 39 vs. 4 of 14; $P < 0.05$) and Maori race (7 of 39 vs. 0 of 14) were more common with DN. Patients with GN had a shorter duration of diabetes (3.8 (SD 2.1) years; $P < 0.001$). Of the 39 patients with DN followed for 25.7 (SD 22.8) months, 17 are dead (8 myocardial infarction, 6 uremia, 2 sepsis, 1 stroke), 9 are on dialysis and 13 are alive (plasma creatinine 0.14 (SD 0.06) mmol/liter). The one and five year cumulative renal survival rates were 76% and 27%, respectively. In patients with IDDM of >10 years duration, retinopathy and proteinuria renal biopsy appears unnecessary to diagnose DN. DN, especially with nephrotic syndrome, has a poor prognosis.

Comparison of a single dose with a five day course of trimethoprim for asymptomatic (covert) bacteriuria of pregnancy. *R.R. Bailey, B.A. Peddie, V. Bishop, Department of Nephrology, Christchurch Hospital, Christchurch, New Zealand.* The benefits of detecting and treating asymptomatic (covert) bacteriuria in pregnancy are well established. Single-dose antimicrobial therapy is now widely used for the treatment of uncomplicated urinary tract infections. Most reported studies with single dose therapy have been done in non-pregnant women. In the latter context, two of the most successful drugs used in single dose regimens have been co-trimoxazole and trimethoprim alone. A prospective, randomized study was undertaken to compare the efficacy of a single 600 mg dose of trimethoprim with a five day course of trimethoprim (300 mg, 24 hr) for the treatment of asymptomatic bacteriuria in women between 16 and 30 weeks gestation. Sixty women with asymptomatic bacteriuria were allocated to treatment, with 27 of 30 being cured with single dose trimethoprim, compared with 24 of 30 given a five day course. One woman vomited the single dose. She was one of the three women who failed treatment with single dose trimethoprim. All three had a normal intravenous urogram. Of the six women who failed a course of treatment with trimethoprim, four had an intravenous urogram and two of these were found to have unilateral reflux nephropathy and one a renal calculus. No detrimental effects on the pregnancy outcome were noted. Single dose therapy should be considered as the treatment of choice for covert bacteriuria in pregnancy.

Calculation of the apparent affinity constants for aluminium and transferrin. *M. Nicholson, J.H. Coates, M. Cochran, Department of Medicine, Flinders Medical Centre, South Australia 5042 and Department of Physical Chemistry, University of Adelaide, South Australia 5000.* Since transferrin is a specific protein carrier for aluminium in the ECF with stoichiometric binding at two sites on the molecule, it is of interest to characterize the apparent affinity constants (K'_a) for the Al-transferrin complex. This can be accomplished by examining the equilibrium concentrations of transferrin, aluminium, and citrate, using the citrate as a competing ligand. The concentration of the Al-transferrin complex can be measured by differential spectrophotometry at 240 nm. Aliquots of sodium hydrogen citrate (20 nmole), and aluminium chloride (20 nmole) were progressively added to a solution of transferrin (100 nmole) at pH 7.4, and ΔA_{240} measured after equilibration. The experiment was repeated at different citrate concentrations giving a curve for each concentration. Knowing the K_a' for aluminium and citrate ions and the aluminium ion hydrolysis constants, it was possible to derive values for the differential molar absorptivity at 240 nm and the Al-transferrin K_a'. The latter were established as $\simeq 10^{13} M^{-1}$. These very high K_a' values between aluminium and transferrin imply that transferrin will act as a sink for the metal in the ECF, inhibiting its removal by any dialysis technique. The concentration of "free" aluminium will always be very small under physiological conditions, except where there is biological alteration of the Al-transferrin complex. The possibility exists that the complex may deliver aluminium to specific sites causing interference with the metabolism of other trace elements.

Sexual dysfunction in home hemodialysis patients. *K.L. Lynn, A. L. Buttimore, B. Hill, Department of Nephrology, Christchurch Hospital, Christchurch, New Zealand.* The incidence of sexual dysfunction was evaluated in home hemodialysis (HHD) patients seen at an annual review. Forty–two HHD patients (15 women, 27 men; 6 diabetics), aged 25 to 70 (mean 47) years, were studied. They had dialysed three times weekly for 8 to 10 hours for 12 to 133 (mean 41) months. None were taking antihypertensives. Thirty–seven patients had a healthy sexual partner. Of the 10 women aged <55 yr, four had amenorrhoea, four had abnormal menstruation and two had normal periods. Twelve of 27 men and two of 15 women reported normal libido. For men with normal libido, plasma testosterone concentration was higher (17.5 [SD 6.4] vs. 12.6 [SD 5.1] nmol/liter; $P < 0.05$). Seven men (26%) had normal potency. Plasma testosterone concentrations were higher (19.2 [SD 5.1] vs. 13.0 [SD 5.6] nmol/liter; $P < 0.02$) and plasma zinc concentrations lower (14.3 [SD 2.1] vs. 16.8 [SD 3.7] μmol/liter, $P < 0.05$) in potent men. Plasma prolactin concentration and age were not significantly correlated with libido or erectile function. Four patients had coitus monthly, three more than monthly, six weekly, four more frequently and 25 never. Twenty–five pairs, five partners and two patients rated their sex lives as satisfactory, while in five pairs both were dissatisfied. HHD patients have a high incidence of sexual dysfunction which appears to be well tolerated.

Nutritional assessment in patients on long–term continuous ambulatory Peritoneal dialysis (C.A.P.D.). *P.J. O'Connell, L.S. Ibels, M.A. Thomas, D.C.H. Harris, J. Kesselhut, K. Heathcote, Department of Renal Medicine, Royal North Shore Hospital, Sydney, N.S.W., Australia.* In order to assess the effects of C.A.P.D. on nutritional status and to see what effects age, sex, and time had on these changes, anthropometric, dietary, fasting biochemical, and hematological studies were performed up to eighteen months after commencing C.A.P.D. There were 66 patients (39 females and 27 males) aged eight to 68 years (mean 46.6 years) and 788 patient months were studied. Age was arbitrarily divided into < 50 years (33 patients) or > 50 years. Results were assessed by using multiple linear regression and multivariant analysis. There was a significant ($P < 0.05$) increase in ideal body weight (mean increase 14%), triceps skinfold thickness (TSF) (mean increase 43%), cholesterol (6.7 ± 1.4 to 7.5 ± 3.0 mmol/liter) and triglycerides (2.7 ± 1.3 to 3.8 ± 2.7 mmol/liter) with time. Ideal weight and triceps skinfold thickness was signifcantly greater in the older patient (> 50 years). TSF and cholesterol were greater in females and midarm muscle circumference (MAMC) was greater in male patients. Urea and urea generation rates were constant, but were significantly greater in males. Serum albumin (37 ± 4 g/liter), absorbed glucose (560 g ± 226), peritoneal protein loss (7.7 g ± 2.9) and serum transferrin (246

± 60 g%) remained constant. Using correlation analysis, ideal weight had a significant correlation with increases in TSF, triglycerides, cholesterol and absorbed glucose. In conclusion, long-term C.A.P.D. is associated with an increase in body fat and often results in a weight increase above ideal body weight. There is an increase in cholesterol and triglycerides which correlates with an increase in ideal body weight.

Nutritional status of home hemodialysis patients. *K.L. Lynn, A.S. Talemaitoga, B.A. Sanders, Department of Nephrology, Christchurch Hospital, Christchurch, New Zealand.* Malnutrition is said to be common in renal failure but there are few studies of home hemodialysis (HHD) patients. We studied 32 HHD patients (23 men), aged 50 (SD 14) years, who had dialysed three times weekly (mean 23.1 hr/wk) for 1 to 138 months. No formal dietary restrictions were imposed. Body mass index (BMI), arm muscle circumference (AMC) and triceps skin fold thickness (TSF) were measured using standard techniques. Diet was assessed by three day dietetic diary and interview. Mean caloric intake was 29.4 (SD 10.7) kcal/kg; 18 (56%) patients had energy intakes less than the 25th percentile for normals. Protein, vitamin C, and folate intakes were above recommended minimum safe intakes. Intakes were less than recommended for calcium in four (13%) patients, iron in one (3%) and vitamin B_{12} in two (6%). One-third of both sexes had BMI (kg/m^2) <25th percentile for normals, but none were <80% of ideal body weight. AMC was normal for all patients but TSF was <60% of standard in eight men (35%) and three women (33%). No anthropometric measurements were correlated with energy, protein, or fat intake. Laboratory tests were not useful in predicting protein intake. Neither nutritional intake nor anthropometric measurements were correlated with the duration of HHD. There was little evidence of malnutrition and wasting in this group of well rehabilitated HHD patients.

Lymphokine (MIF) production by glomerular T-lymphocytes in experimental glomerulonephritis. *N.W. Boyce, P.G. Tipping, S.R. Holdsworth, Monash University Department of Medicine, Prince Henry's Hospital, Melbourne, 3004, Australia.* Glomerular T-lymphocyte infiltration has recently been demonstrated to precede glomerular macrophage influx in a preimmunized model of anti-glomerular basement-membrane antibody-induced glomerulonephritis (antiGMB-GN). In the current study, the functional role of these glomerular T-lymphocytes in directing macrophage localization was sought by measuring their production of macrophage migration inhibition factor (MIF). MIF activity in supernatants from culture isolated glomeruli was measured in a conventional capillary tube bioassay. Glomerular T-lymphocytes (OX19 positive cells) were maximal (1.95 ± 0.19 cells/glomerular cross section, c/gcs) 24 hours after injection of antiGBM antibody into sensitized animals. Seventy-two hours after antibody injection, T-lymphocyte numbers were reduced (1.02 ± 0.14 c/gcs) while macrophage accumulation was maximal (at 24 hrs 4.2 ± 1.3 macrophages /glomerulus (m/g) : at 72 hrs 19.8 ± 3.7 m/g). MIF activity was only detected in supernatants from T-lymphocyte infiltrated glomeruli; (12 hrs 40.8 ± 4.32% migration inhibition: 24 hrs 45.11 ± 4.11% migration inhibition: 48 hrs 38.24 ± 3.53% migration inhibition: 72 hrs 20.86 ± 3.85% migration inhibition, all $P < 0.05$). Control glomeruli from normal animals, preimmunized animals given normal sheep globulin, preimmunized animals given anti-GBM antibody and cyclosporin A and non-preimmunized animals given antiGBM antibody did not contain glomerular T-lymphocytes and their supernatants contained no MIF activity. This data indicates that the glomerular T-lymphocytes in preimmunized antiGBM GN are sensitized cells which release MIF, and thus may direct glomerular macrophage localization in this model of antibody induced glomerulonephritis.

Renal dendritic cell accumulation in lupus nephritis. *D.H. Hooke, A.B. Suleiman, N.M. Thomson, R.C. Atkins, Departments of Nephrology, Prince Henry's Hospital, Melbourne, Australia, and Hospital Besar, Kuala Lumpur.* We have recently characterized the glomerular and interstitial leucocytic infiltrate in human glomerulonephritis using monoclonal antibodies as specific markers of leucocyte subsets. Lupus nephritis has a marked interstitial leucocytic infiltrate and the current study examines the renal interstitial dendritic cell (RIDC) in biopsies from patients with lupus nephritis. Since dendritic cells in other organs are known to play an important role in antigen presentation and immune response induction, this study was designed to determine whether intrinsic RIDC accumulation is a feature of the immune response in this disease. Renal tissue from 27 individuals (13 normal kidneys and 14 lupus nephritis biopsies) was stained by a three-layer immunoperoxidase technique using monoclonal antibodies to different antigenic determinants of the leucocyte common molecule. The first (10.89.4) labels all nucleated hemopoietic cells including RIDCs. The second, (PHM1), labels all nucleated hemopoietic cells but is not expressed on RIDCs. The RIDC population was defined by (10.89.4 +ve) cells minus (PHM1 +ve) cells. Cell numbers are expressed as cells/mm^2 ± SEM. When compared with normal renal tissue, there was a significant increase in both the total interstitial cell population (10.89.4 +ve) 260 ± 44 vs. 68 ± 2.8 ($P < 0.001$) and the infiltrating leucocytes (PHM1 +ve) 162 ± 32 vs. 36 ± 5 ($P < 0.01$). There was a marked increase in the interstitial dendritic cell population 98 ± 16 vs. 36 ± 5 ($P < 0.01$), however the proportion of the total interstitial cells comprised of cells of dendritic phenotype was the same in the interstitium in normals and lupus nephritis. Dendritic cells in the renal interstitium therefore accumulate in proportion to the degree of interstitial leucocytic infiltration. Whether this is due to proliferation of intrinsic RIDCs or infiltration by circulating dendritic cells is yet to be determined. It is probable however that these cells, which are potent accessory immune cells in other sites, play a role in the immunopathogenesis of the interstitial lesion in human lupus nephritis.

Inhibition of idiotypic anti-glomerular basement membrane antibodies with heterologous anti-idiotypic antibodies using a splenic PFC assay. *J.A. Savige, C.M. Lockwood, MRC Clinical Immunology Unit, Royal Post-graduate Medical School, London, United Kingdom.* We have established a direct plaque-forming cell (PFC) assay using spleens harvested from BALB/c mice immunized with human glomerular basement membrane (HGBM) (50 mcg in CFA × 3) in order to detect the presence of heterologous anti-idiotypic antibodies to anti-HGBM antibodies. Briefly, 50 μl of washed spleen cells (10^9 ml^{-1}) were incubated for 1 hour at 37°C with 10 μl 10% RBC coated with HGBM (using the $CrCl_3$ method), 10 μl 1:2 guinea pig complement and 10 μl RPM in Cunningham Chambers. A heterologous anti-idiotypic antibody was prepared by C. Savage by repeatedly immunizing a NZW rabbit with affinity-purified human anti-GBM antibody. After extensive absorption against normal mouse serum, IgG extracts were absorbed and eluted from a $^+$MCA (anti-HGBM) or $^-$MCA column. Ten μl of these neutralized eluates, with a concentration of 10^{-2} mg ml^{-1} were added to the PFC assay. The eluate from the +MCA columns resulted in inhibition in five out of five assays (38% to 88% decrease total number of plaques, compared with the number seen with eluates from −MCA columns). Eluates were prepared in an identical fashion for IgG extracts from acute (3) and convalescent sera (3) of patients with anti-GBM antibody disease. (Anti-GBM antibodies were first removed from the acute phase IgG). No inhibition was demonstrated when 10 μl of eluates (10^{-2} mg ml^{-1}) from $^+$MCA and $^-$MCA columns were added to the direct PFC (×2). The inability to demonstrate inhibition by a putative human anti-idiotypic antibody using this assay system may be because the concentration of anti-idiotypic antibody was too low to be detected in this assay, or because of $^+$MCA is a cross-reactive idiotype of limited distribution in humans.

Serum sickness nephropathy in the rat using cationized albumin. *B.F. Murphy, A.J.F. d'Apice, G.J. Becker, P.S. Kincaid-Smith, The Royal Melbourne Hospital, Melbourne, Australia.* Kamil and Border have demonstrated mesangial as well as capillary loop deposits on immunofluorescence (IF) and electron microscopy (EM) in rats injected with cationic albumin as distinct from rabbits who develop a pure membranous nephropathy. We have obtained similar but much larger lesions by increasing the pre-immunization. Sprague-Dawley rats were pre-immunized with human serum albumin (HSA) in adjuvant using different regimes which resulted in either high or low titers of precipitating antibodies. Daily intravenous injections of 2 mg of cationized HSA (cHSA) were then commenced. Rats with low titer anti-HSA antibodies prior to i.v. injection developed massive proteinuria five days after commencement of i.v. cHSA. Subepithelial, subendothelial, and mesangial deposits of HSA, IgG and C3 were seen on IF at five days and increased over 25 days. At day 25, light microscopy (LM) revealed scattered subepithelial deposits and early spike formation;

extensive subepithelial and some subendothelial deposits were seen on EM. In rats with high titer antibodies, proteinuria did not develop until 10 to 14 days after commencement of i.v. injection. However, by 25 days there were gross confluent subendothelial deposits together with widespread subepithelial and mesangial deposits clearly visible on LM. Further groups of rats given 5 mg i.v. cHSA daily showed similar findings except for earlier development of proteinuria and deposits. Control rats pre-immunized with adjuvant alone then injected with cHSA developed no disease.

Antigen identification in glomerulonephritis using monoclonal antibodies. *B.F. Murphy, A.J.F. d'Apice, G.J. Becker, P.S. Kincaid–Smith. Royal Melbourne Hospital, Melbourne, Australia.* Monoclonal antibodies have been raised against components of glomerular immune deposits in experimental and human glomerulonephritis (GN). An accelerated model of chronic serum sickness in the rat using cationized human serum albumin (HSA) was employed to obtain renal tissue with capillary loop and mesangial immune deposits. Lesions ranging from very early deposits seen only on immunofluorescence to gross deposits clearly visible on light microscopy were produced. Glomeruli were then isolated by graded sieving, and Balb C mice were immunized twice in adjuvant with approximately 4,000 washed whole glomeruli or a preparation of glomerular basement membrane (GBM) obtained by ultrasonification. Mice spleens were harvested three days after an intraperitoneal boost of GBM and fused with SP2/0 myeloma cells. Colonies were screened by ELISA at 10 days for mouse immunoglobulin production and for reactivity against HSA. Anti-HSA monoclonal antibodies were produced from all technically successful fusions irrespective of the amount of deposit in immunizing tissue or whether whole glomeruli or GBM were used for immunization. Glomeruli from a human kidney with membranous glomerulonephritis have also been used for immunization and fusion. Colonies were screened histologically for antibodies reactive against the GBM deposits in the immunizing kidney. Eighteen such antibodies have so far been produced. One has been identified as reactive against C3 and the others are yet to be characterized.

Identification of circulating immune complex (CIC) constituents by combined thin gel isoelectric focusing (IEF) and immunoblot analysis. *T.J. Neale, J.C. Muir, B. Drake, Department of Medicine, Wellington Clinical School of Medicine, Wellington, New Zealand.* Assays based on physicochemical and/or biological properties of CICs allow their quantitation, but constituent components are rarely identified. We applied sensitive analytic techniques to precipitated complexes from a patient with *Candida albicans* thoracic vertebral osteomyelitis, and end–stage renal failure due to lupus nephritis. *Candida albicans* was present in biopsy material from the vertebral lesion but not in blood cultures, or in bone after four weeks antifungal therapy. CIC measured by 2% polyethylene glycol (PEG) precipitation, and C1q and anti-C3 microELISA assays peaked during the illness, falling to background following antifungal therapy and surgical excision with bone grafting. *Candidal* precipitins were measurable three months prior to presentation and throughout treatment but were undetectable eight weeks following surgery. Analysis of PEG-precipitated CIC by thin gel IEF (pH 3.5-10) on polyacrylamide or agarose revealed homology between two anodal bands and reference *Candida* mannoprotein antigens (Immunomycologics), with approximate molecular weights of 52 to 60 kd. Nitrocellulose press blots and Western transblots of IEF-separated CIC probed with specific antisera to mannan, *Candida* somatic antigens, C1q and C3 indicated their contribution to the CICs. Blots of *Candida* antigens were probed with peak precipitin serum to define the reactivity of free antibody. These sensitive techniques were applicable to CIC component identification where the likely origin of antigen was known. It is intended to extend their use to unknown systems in patients with glomerulonephritis.

Verapamil (V) slows the progression of experimental chronic renal failure (CRF). *D.C.H. Harris, W.S. Hammond, T.J. Burke, R.W. Schrier, Department of Medicine, University of Colorado School of Medicine, Denver, Colorado, USA.* V ameliorates ischemic acute renal failure (ARF) and chronic V administration reduces the magnitude of uremic nephrocalcinosis (NC) found three weeks after subtotal nephrectomy (SNX). In the present study, the effect of chronic V on the progression of renal injury after SNX was examined. V (0.1 μg/g body wt sc bid) or saline (S, 0.1 ml sc bid) were administered from day 10 after SNX for up to 23 weeks to 10 pairs of rats, which were matched initially for renal functional impairment and body weight. Rats were pair fed in metabolic cages and metabolic parameters were measured every two weeks. Just prior to the uremic death of an S treated rat, both members of the pair were electively sacrificed. At sacrifice, V rats had a lower serum creatinine (SCr 0.202 vs. 0.265 mmol/liter, $P < 0.05$) and a higher creatinine clearance (CCr 318 vs. 164 μl/min, $P < 0.05$) than S treated rats. Proteinuria was similar in the two groups (294 vs. 354 mg/24 hr, NS). Glomerular sclerosis, NC, and total renal damage were more severe in S treated rats. Renal and myocardial Ca content were higher in S rats (102.3 and 14.0 nmol/mg dw, respectively) than in V rats (39.4 and 7.2, $P < 0.05$). In a second group of rats ($N = 22$), survival was studied. Each week from week seven, survival was significantly better for V rats ($P < 0.0025$ at week 14). SCr was higher at week 10 (0.149 vs. 0.097 mmol/liter, $P < 0.05$) in S rats. Mean arterial pressure measured at least 45 minutes after V or S was not significantly different between the two groups. Thus, chronic V administration delays the progression of renal failure, lessens the magnitude of histological damage and NC, and improves survival in this model of CRF. This protective effect of V is independent of any antihypertensive effect.

Parameters for the evaluation of renal phosphate (P) handling and of parathyroid (PT) activity in children. *H. Stark, B. Eisenstein, M. Davidovitz, H. Kaufman, Pediatric Nephrology Unit and Endocrine Laboratory, Beilinson Medical Center, Israel.* Evaluation of renal handling of P and PT activity in children is hampered by an absence of normal standards for various parameters in the pediatric age–groups. Serum PTH (C-terminal), urinary cAMP (UcAMP) and tubular reabsorption of P (TP) were determined in 41 healthy children aged one month to 16 years. TP was measured as P filtered—P excreted (per dl glomerular filtrate)

$$= S_p - \frac{U_p \cdot S_{creat}}{U_{creat}} \text{ mg/dl.}$$

We prefer this directly measured parameter to the commonly used theoretical TmP/GFR, which is derived from a nomogram based on adult data.

Age (yrs)	TP (mg/dl GF)	PTH (ng/ml)	cAMP (nM/dl GF)
1/12–2	5.1 ± 0.9	0.38 ± 0.17	2.5 ± 1.5
2–5	[a]4.6 ± 0.6	0.30 ± 0.15	2.0 ± 0.7
5–10	4.6 ± 0.6	0.38 ± 0.15	1.7 ± 0.4
10–16	[a]4.2 ± 0.6	[a]0.23 ± 0.10	2.2 ± 0.7
Adult values	2.9 ± 0.2	0.44 ± 0.22	3.0 ± 0.8

[a] Significantly different from preceding value.

Values for children were significantly different from adults. Correlation was found between TP and cAMP: $TP = 5.5 - 0.5 \times U_{cAMP}$ ($r = 0.45$, $P < 0.05$), with a scatter of ± 0.6 mg/dl (± 1 SD). The absence of significant correlation between TP and PTH suggests the latter (as measured here) is not a sensitive parameter of PT activity. The use of these data to evaluate respective influences of tubular function and of PT activity is demonstrated in children with various disorders of P metabolism.

Calcitriol levels in moderate chronic renal failure. *B.G. Hutchison, R.L. Prince, J. Kent, G.N. Kent, R.W. Retallack, Departments of Renal Medicine, Medicine and Endocrinology and Diabetes, Sir Charles Gairdner Hospital, Nedlands, 6009, Australia.* The role of calcitriol (1,25D) in calcium (Ca) homeostasis in early chronic renal failure (CRF) is still controversial. Ca deprivation has been used to study this area. Six patients with a mean glomerular filtration rate (GFR) of 43 ml/min (range 27 to 80) and six age and sex matched normal subjects with a mean GFR of 122 ml/min (range 94 to 189) were studied. Ca deprivation was induced by consumption of a low-Ca diet supplemented with oral cellulose phosphate. Samples were collected on two baseline days (days −4 and 0) and during Ca deprivation which continued for seven days. 1,25D and immunoreactive parathyroid

hormone (iPTH) were measured using previously described methodology.

	iPTH (pmol/liter)		1,25D (pg/ml)	
	Normal	CRF	Normal	CRF
Baseline −4	20 ± 4	197 ± 68	35.7 ± 3.1	19.5 ± 3.4
Baseline −0	27 ± 7	232 ± 78	46.1 ± 4.6	21.3 ± 4.0
Day +2	26 ± 5	236 ± 64	67.1 ± 5.9	26.4 ± 3.4[b]
Day +4	25 ± 2	259 ± 71[a]	53.7 ± 4.2	31.9 ± 5.2[a]
Day +7	26 ± 4	285 ± 87	49.9 ± 5.3	29.6 ± 4.4[a]

	1,25D/GFR	
	normal	CRF
Baseline −4	0.3 ± 0.1	0.5 ± 0.1
Baseline −0	0.4 ± 0.1	0.5 ± 0.1
Day +2	0.6 ± 0.1	0.7 ± 0.1[b]
Day +4	0.4 ± 0.1	0.8 ± 0.1[a]
Day +7	0.4 ± 0.1	0.8 ± 0.1[a]

Results are mean ± SEM.
[a] $P < 0.05$.
[b] $P < 0.02$
Cf Baseline.

iPTH levels were much higher in CRF patients than normals and rose during the study. Basal 1,25D levels were lower in CRF patients than normals but nevertheless rose significantly with Ca deprivation. When 1,25D levels were corrected for the reduced GFR, there was no difference in peak stimulated 1,25D between normals and CRF patients. Throughout the study in CRF patients, plasma phosphate was high normal and TmP was very low, suggesting relative renal phosphate retention. *Conclusions*: (*1*) in moderate CRF 1,25D is markedly reduced. (*2*) during Ca deprivation, 1,25D rises, indicating secretory reserve. When corrected for GFR, stimulated 1,25D is the same as normal, despite high PTH. (*3*) The relative resistance of 1,25D to PTH stimulation may be related to altered renal phosphate handling. (*4*) This study suggests a significant role for 1,25D early in the development of CRF-related disturbances of Ca homeostasis.

Renal failure does not impair elimination of morphine. *K.L. Lynn, D. Winter, D.F. Woolner, E.J. Begg, T.J. Frendin, G.F. Wright, Department of Nephrology, Christchurch Hospital, Departments of Anaesthetics and Medicine, Christchurch Clinical School, Department of Chemistry, University of Canterbury, Christchurch, New Zealand.* Recent studies using radioimmunoassay suggest that the kidney and not the liver is the main site of opioid metabolism. We have used gas chromatography–mass spectrometry (GC-MS) to assess the elimination of morphine and its glucuronides, after IM papaveretum (~50% anhydrous morphine), in four men (one anephric), aged 34 to 60 years, on hemodialysis and three normal men, aged 34 to 41 years. Each patient had a forearm fistula, normal liver function tests and was studied on a non-dialysis day. Papaveretum (0.25 mg/kg body wt) was injected in the deltoid muscle (fistula arm in patients). Venous blood was obtained from the contralateral arm at intervals up to 24 hours. The pharmacokinetics of morphine measured using GC-MS were:

		t½ abs hr	t½ elim hr
Healthy volunteers	Mean	0.09	2.17
	SEM	0.03	0.13
Renal failure	Mean	0.05	1.21
	SEM	0.02	0.20
	P	0.03	0.03

	AUC μg/liter · hr^{-1}	CL liter/kg/h^{-1}	V liter/kg
Healthy volunteers	134.62	1.28	4.01
	14.32	0.14	0.43
Renal failure5.67	101.54	1.67	3.05
	0.19	0.55	
	0.06	0.19	0.24

The patients with renal failure had significantly shorter t½ (abs) and t½ (elim) for morphine and eliminated the glucuronides slowly. These results suggest that renal failure does not impair the elimination of morphine.

Anti-glomerular basement membrane glomerulonephritis (AGBMGN) associated with membranous transformation (MT): A report of five cases. *J.P. Dowling, B.U. Ihle, G. Becker, S.R. Holdsworth, D.C. Mathews, P. Kincaid-Smith, Departments of Anatomical Pathology and Nephrology, Royal Melbourne Hospital and Department of Medicine, Prince Henry's Hospital, Melbourne, Australia.* Of a group of 22 patients with confirmed AGBMGN, five were noted to develop MT in association with diffuse crescentic glomerulonephritis. A summary table of clinical details, investigations and progress is as follows:

	Presentation				Creatinine	
Pt. no, initials	age/sex (yrs)	mth/yr	Hematuria	Proteinuria g/24 hrs	mmol/liter pres[1]	Curr[2]
1/MH	20/F	6/'80	Macroscopic	+++	0.48	0.10
2/ST	19/F	12/'81	Macroscopic	0.4	1.3	0.38
3/KL	47/M	11/'83	Macroscopic	−[a]	1.43	—
4/GD	18/M	10/'84	Macroscopic	+++	0.81	0.19
5/KG	17/F	12/'84	Macroscopic	6.5	0.12	0.09

[a] No urine obtained for estimation.
[1] At presentation.
[2] Current (Oct, 85).

All patients showed the presence of AGBM antibodies on radioimmunoassay. Patient 1, MH, subsequently was found to have an anti-nuclear factor and a raised DNA binding. Only one patient, KG, had haemoptysis. All patients received therapy with a combination of cyclophosphamide and prednisolone with anticoagulation and plasmapheresis. Four patients responded well to these measures with two (MH and KG) having a serum creatinine currently within normal limits and two (GD and ST) having persistent impairment of renal function. Patient 3, KL, progressed rapidly to end-stage renal failure, requiring transplantation; graft function is at present excellent. All patients showed diffuse crescentic GN with at least 85% crescents on initial biopsy. In three, (ST, KL and KG) MT was noted on the first biopsy and was diffusely developed in KL and KG and focal in ST. Focal MT was found in follow-up biopsies of MH and GD. The distribution of MT has remained similar in further follow-up biopsies of MH, ST, GD and KT. A recent transplant biopsy of KL revealed mild interstitial rejection and segmental glomerular necrotizing lesions; radioimmunoassay for AGBM antibodies was negative. Varying degrees of proteinuria persist in the patients not transplanted. Despite this, the outcome in this group of patients appears to be governed more by the activity of the AGBM component of the renal lesion than the MT.

The hypertensive effect of cyclosporine A in sheep. *E.H. Mills, J.P. Coghlan, D.A. Denton, J.G. McDougall, C.D. Spence, J.J. Tresham, B.A. Scoggins, J.A. Whitworth, Howard Florey Institute of Experimental Physiology & Medicine, and Royal Melbourne Hospital, University of Melbourne, Parkville, 3052, Australia.* The immunosuppressive drug cyclosporine A (CYA) has been reported to be associated with hypertension in renal and cardiac transplanted subjects. This study examines the haemodynamic, renal and hormonal effects of CYA in sheep. Six conscious sheep (body wt 35 to 45 kg) were infused i.v. 12 mg/kg/day CYA for five days. Mean arterial pressure (MAP) was increased from days 1 to 5, 73 ± 1 mm Hg control to 90 ± 4 mm Hg on day 5 of CYA infusion ($P < 0.001$). Heart rate increased on days 1, 2, 3 and 5 of CYA, 58 ± 3 beats/min control to 75 ± 5 beats/min day 5 ($P < 0.01$). Cardiac output did not change, but calculated total peripheral resistance was elevated on days 1, 3 and 4, 16 ± 1 mm Hg min/liter control to 21 ± 2 mm Hg min/liter day 4 ($P < 0.001$). Stroke volume decreased, 86 ± 7 ml/beat control to 68 ± 8 ml/beat on day 5 ($P < 0.001$). There was no change in plasma [Na], but there was a decrease in plasma [K], 4.3 ± 0.1 mmol/liter control and 4.0 ± 0.1 mmol/liter on day 5 ($P < 0.001$). There was a fall in water intake on days 3, 4 and 5, 2.02 ± 0.12 liter/day control and 1.65 ± 0.28 liter/day 5 ($P < 0.05$). Urine volume did not change with CYA infusion. Urinary Na excretion decreased on days 2

to 5 of infusion. Plasma renin concentration was unchanged by CYA. One of the six animals developed reversible oliguria over the first two days of CYA infusion, and the infusion was terminated. CYA did not change GFR but effective renal plasma flow increased 429 ± 18 to 559 ± 44 ml/min on day 5 ($P < 0.05$). There was no change in filtration fraction, renal vascular resistance, renal blood flow or body weight. These results indicate that CYA reproducibly produces significant hypertension, even in the absence of a reduction in renal function. The resistance mediated hypertension is not simply a consequence of nephrotoxicity.

Atrial natriuretic peptide (ANP) release with volume changes in chronic renal failure. *R.J. Walker, C.P. Swainson, Department of Nephrology, Christchurch Hospital, Christchurch, New Zealand.* The effect of ECF volume changes on the release of ANP was studied in nine patients (six male, three female) on chronic hemodialysis (no antihypertensive medication) 48 hours after their last dialysis. Patients with ischemic heart disease or diabetes mellitus were excluded. Ultrafiltration was adjusted so that body weight fell 4% over two hours, then saline was steadily infused until weight returned to the starting point over two hours, plus a further 30 minute infusion. Blood was drawn at 30 minute intervals for ANP, aldosterone, electrolytes and creatinine, and blood pressure, pulse and weight were recorded. The initial ANP ranged from 30 to 112 pmol/liter. During volume reduction ANP fell by a mean of 28.8% (SD 13.7), but during volume expansion there was a much larger rise in ANP, mean 99% (SD 69). There was no significant change in plasma potassium, creatinine, or aldosterone concentrations. During volume expansion ANP release was rapid and quantitatively much larger than the fall from baseline seen with volume reduction. These results confirm that ANP is released in response to acute volume expansion, which may be mediated through stretch receptors in the atria.

Effect of atrial natriuretic factor on vasopressin release. *K. Ogawa, C.I. Johnston, Monash University Department of Medicine, Prince Henry's Hospital, St. Kilda Road, Melbourne, 3004, Australia.* Atrial natriuretic factor (ANF) is a circulating peptide hormone stored in specific atrial granules. The biological actions of ANF (natriuresis, diuresis, vasodilation) are opposite to those of arginine–vasopressin (AVP). This study was designed to investigate the effects of intracerebroventricular (ICV) or intravenous (i.v.) injection of ANF (rat α atrial natriuretic polypeptide, Peninsula Lab, 28AA) on plasma AVP, plasma renin activity (PRA), blood pressure (BP), and pulse rate (PR) in conscious rats. Studies were performed in conscious unrestrained rats with chronic indwelling lateral ventricular cannulae and venous and arterial catheters. ANF (0.3 nmol/kg ICV, 0.1 nmol/kg i.v. or 2.5 nmol/kg i.v.) was injected into 24 hour water–deprived or normally–hydrated Long–Evans rats. Plasma AVP and PRA were measured by radioimmunoassay. No changes were observed in plasma AVP and PRA following ANF ICV injection. No changes were found in BP and PR after four different doses of ICV ANF injection (0.01 to 0.3 nmol/kg). No significant changes were observed in plasma AVP after i.v. ANF injection (0.1 or 2.5 nmol/kg) either in hydrated or dehydrated rats. However rehydration caused a prompt fall in AVP levels to normal within 30 minutes. The lower dose of ANF was not associated with any haemodynamic effect, but a dose related fall in blood pressure was seen with the high dose of ANF. ANF administration (2.5 nmol/kg i.v.) decreased PRA in both hydrated and dehydrated rats. We conclude that neither i.v. nor ICV ANF administration affect AVP release in conscious rats.

Enhancement of the renal but not hemodynamic effects of atrial natriuretic peptide in conscious sheep. *D.G. Parkes, N.A. Yates, J.P. Coghlan, D.A. Denton, J.G. McDougall, B.A. Scoggins, Howard Florey Institute, University of Melbourne, Parkville, Victoria 3052, Australia.* Atrial natriuretic peptide (ANP) has diuretic, natriuretic and vasodepressor activity in rats, dogs, sheep, and man. In normal sheep the dose threshold for hemodynamic effects is less than that for effects on the kidney. To examine whether volume status influences the physiological responses to ANP the peptide has been infused in isovolemic, hypervolemic, and ACTH hypertensive conscious sheep. ANP (1-28) was infused intravenously at 100 μg/hr for 60 minutes into: (*1*) normotensive isovolemic sheep; (*2*) sheep in which blood volume had been expanded 30% with dextran; and (3) sheep with ACTH hypertension (5 μg/kg/day for five days) and in whom plasma volume is increased. The renal effects were also examined in sodium (Na) depleted sheep (48 hr uncompensated parotid salivary loss). In isovolemic sheep, ANP reduced blood pressure (MAP) by 3 ± 2 mm Hg ($P < 0.05$) due to a fall in cardiac output. Neither volume expansion nor ACTH treatment produced a significant change in the effects on MAP. In contrast, in volume–expanded sheep ANP increased urine flow by 8.9 ± 2.3 ml/min ($P < 0.01$) compared with 0.3 ± 0.1 ml/min in isovolemic animals. Urinary Na excretion increased by 688 ± 130 μmol/min volume expanded compared with 58 ± 10 μmol/min isovolemic. A similar enhancement of the renal effects was seen in ACTH treated sheep. In Na depleted sheep the renal effects of ANP were reduced. In summary, these studies show that the renal response to ANP is modulated by the volume status of the animal.

Mechanism of Cyclosporine A stimulation of renal cortical slice renin secretion. *G. Duggin, V. Lazarro, C. Baxter, B. Hall, J. Horvath, D. Tiller, Department of Renal Medicine, Royal Prince Albert Hospital, Camperdown, Australia.* The intrarenal renin angiotensin system is thought to play a major role in the intrarenal control of glomerular filtration rate (GFR). CSA treated patients show a significant drop in GFR and this decrease is usually rapidly reversed on cessation of the drug, suggesting that CSA is directly or indirectly affecting the intrarenal control fo GFR. Studies were undertaken in Firth Wistar rat renal cortical slices. The stimulation of renin release by CSA was studied by incubating renal cortical slices with the drug and determining the renin activity in the incubation media. CSA 8×10^{-6} mol stimulated renin secretion significantly above control, although not to the same extent as Isoproterenol. Angiotensin II and 60 mmol KCl, which inhibited renin release, were not overcome by CSA. CSA stimulated renin release was blocked by the beta adrenoreceptor antagonists Timolol and Atenolol. As CSA is not a beta agonist, this would suggest that CSA indirectly affects the beta adrenoreceptors, perhaps by the local release of noradrenaline.

Renal functional effects of ACTH and hydrocortisone administration in man. *J.A. Whitworth, J.M.C. Connell, A.F. Lever, R. Fraser, Department of Nephrology, Royal Melbourne Hospital, Melbourne, Australia, and MRC Blood Pressure Unit, Glasgow, Scotland, United Kingdom.* Administration of ACTH or glucocorticoid hormones has been variously reported to increase renal plasma flow (ERPF) and/or glomerular filtration rate (GFR) in a variety of species. The present study examines the effects on renal function of ACTH (0.5 mg I/M 12 hourly) or hydrocortisone (50 mg 0 6 hourly) in six normal men. Subjects were maintained on 150 mol/day Na and 70 mmol/day K diet for 11 days. After four control days, ACTH or hydrocortisone was given for five days. Urine volume, Na, and K excretion and creatinine clearance were measured daily. Renal function tests were performed prior to and on the final day of treatment. GFR was measured by inulin clearance and ERPF and PAH clearance, before and after infusion of angiotensin II at 2, 4 and 8 ng/kg/min. ACTH produced urinary sodium retention (control 135 ± 8, ACTH 36 ± 12 mmol/day, $P < 0.001$) and an increase in urinary potassium excretion (control 67 ± 3, ACTH 90 ± 4 mmol/day, $P < 0.01$) but no change in urine volume or creatinine clearance. Inulin clearance increased from 142 ± 8 to 200 ± 16 ml/min ($P < 0.01$) but there was no change iN ERPF. Filtration fraction rose from 18.7 ± 1.1 to 26.1 ± 0.9% ($P < 0.001$). Angiotensin II produced dose dependent falls in ERPF both before and after ACTH treatment. GFR fell at high dose only and filtration fraction increased. Hydrocortisone produced initial urine sodium retention only. Urine volume and creatinine clearance were unchanged. Inulin clearance rose from 141 ± 11 to 160 ± 13 ml/min ($P < 0.001$). Renal plasma flow was unchanged and filtration fraction fell. Angiotensin infusion produced results similar to those seen in the ACTH study. Thus both ACTH and hydrocortisone produced urinary sodium retention and increases in inulin clearance and filtration fraction. Renal plasma flow and creatinine clearance were unchanged. The latter, thus, is an unreliable measure of GFR during steroid administration. Angiotension II administration produced substantial falls in renal plasma flow, but a rise in filtration fraction tended to maintain GFR.

Comparison of calcitonin and parathyroid hormone on renal calcium and magnesium transport in the rat. *S.L. Carney, University of*

Newcastle, Newcastle, N.S.W., Australia. There is now good evidence that calcitonin (CT) can facilitate renal calcium and magnesium reabsorption within the thick ascending limb of Henle's loop like parathyroid hormone (PTH). While the cellular mechanism of action is unclear, CT and PTH dependent adenylate cyclase activities within the mammalian distal nephron are also similar and concurrent administration of CT and PTH does not produce an additive effect on cyclic AMP production. This suggests the presence of a single pool of hormone–dependent cyclase activity which responds equally to both CT and PTH. Clearance studies were performed on anesthetized thyroparathyroidectomized rats infused with a calcium Ringer solution to see if these biochemical observations could be reproduced at a biological level. PTH (2.5U/100g) reduced the fractional excretion of calcium from 9.8 ± 0.6 to 5.1 ± 0.6% ($P < 0.01$) and CT (0.15U/100g) also produced a comparable fall in the excretion of calcium (4.1 ± 0.6%). Administration of both CT and PTH was associated with a fractional calcium excretion of 3.0 ± 0.8% which was significantly less than that observed with PTH alone ($P < 0.05$). Since there is evidence that hypercalcemia associated with PTH administration directly reduces renal calcium reabsorption submaximal concentrations of PTH and CT were simultaneously given to a further group of rats and the fractional excretion of calcium was 3.6 ± 0.9%. Magnesium data were similar to that of calcium. These results combined with earlier in vitro data suggest that PTH and CT act upon the same renal transport site to facilitate calcium and magnesium transport.

Physiological role of angiotensin-II in the control of baroreflex sensitivity. *M.G. Garner, A Phippard, P.J. Fletcher, J. Maclean, G. Duggin, J. Horvath, D. Tiller, Hypertension and Cardiology Units, Royal Prince Alfred Hospital, Camperdown, Australia.* Studies of the effect of angiotensin II (AII) on baroreflex function have failed to determine its physiological significance. Species differences, variable study methods and failure to control for other factors such as plasma volume (PV), sodium (Na) status, and direct AII effect on arterial pressure (BP) have all contributed to conflicting results. In this study, baroreflex function was examined in four adult male baboons (Papio hamadryas) with chronic arterial and venous catheters, during manipulation of the renin angiotensin system. Baroreflex sensitivity was assessed by duplicate determinations of the slope between heart rate (HR) and BP, during paired intravenous injections of phenylephrine (PHE) and glyceryl trinitrate (GTN). On high salt diet (100 mmol Na/day) slope was assessed before and during graded AII infusion (10 & 20 ng/kg/min) which raised BP by 20 ± 10 and 32 ± 12 mm Hg. To separate the direct effects of AII from indirect effects due to the rise in BP, assessment of slope during AII infusion was repeated on a separate day with simultaneous infusion of GTN to prevent the rise in BP. On low salt diet (5 mmol Na/day) slope was assessed before and after captopril (1 mg/kg & 5 mg/kg intravenously) which produced graded suppression of endogenous AII and lowered BP by 5 ± 4 and 10 ± 6 mm Hg. This protocol was repeated on a separate day with simultaneous infusion of PHE to prevent the fall in BP. Changing sodium intake had no effect on plasma volume, basal BP, HR or slope. AII infusion caused a significant decrease in slope ($P < 0.01$) which was still apparent after control of acute hypertension. AII antagonism caused a smaller but still significant increase in slope ($P < 0.05$), still apparent after prevention of acute hypotension. The data suggests that physiological variations in AII levels have a small effect on sensitivity of the baroreflex arc independent of its effects on blood pressure.

Somatostatin may also modulate collecting duct water permeability in the absence of arginine vasopressin. *C. Ray, S.I. Carney, A.H.B. Gillies, Faculty of Medicine, University of Newcastle, Newcastle, Australia.* Recent in vitro experiments in our laboratory supported earlier evidence that somatostatin inhibits the antidiuretic action of arginine vasopressin in the mammalian collecting duct. At the same time somatostatin inhibited basal water permeability (3.18 ± 0.14 compared with 3.75 ± 0.09 μm/sec; $P < 0.05$) at concentrations of 10^{-9}M but not at higher concentrations (10^{-8}, 10^{-7}M). Therefore clearance studies in water diuretic anesthetized wistar rats were performed. Somatostatin (30 μg bolus and 60 μg/hr) increased urine volume from 132 ± 10 to 163 ± 8 and 160 ± 11 μl/min ($P < 0.01$) without altering urinary solute excretion. However, increasing the somatostatin concentration (150 μg bolus and 600 μg/hr) did not significantly alter urine flow or solute excretion when compared to control values. Glomerular filtration rate, urinary electrolyte excretion, and papillary solute concentrations were unaltered by somatostatin. In vivo and in vitro evidence that somatostatin can alter both basal and arginine vasopressin stimulated water permeability requires further work to evaluate its significance in the control of body water metabolism.

Circulating inhibitors of Na-K-ATPase respond to changes in osmolality rather than volume. *R.M. Wellard, W.R. Adam, Renal Unit, Repatriation General Hospital, W. Heidelberg 3081 Victoria, Australia.* The search for natriuretic factors (circulating inhibitors of Na-K-ATPase being a contender for natriuretic factor) has centered around a physiological role to prevent extracellular volume overload following excess sodium ingestion and a pathophysiological role in hypertension. However water deprivation is a more likely homeostatic insult than sodium excess and is associated with an increased sodium excretion, presumably a protective mechanism against hypernatremia (and/or hyperosmolality). In this study we look at the effects of plasma from control, dehydrated, rehydrated, low and high sodium diet rats on Na-K-ATPase and rubidium (Rb) transport in guinea pig renal tubules.

	Group	Na-K-ATPase % of control	Rb transport % of control	Plasma Na mmol/liter
A. (i)	Control	100 ± 17 (16)	100 ± 14 (8)	126 ± 2.2 (16)
(ii)	Dehydrated	86 ± 12 (16)[a]	76 ± 18 (7)[a]	130 ± 1.4 (16)[a]
(iii)	Rehydrated	100 ± 15 (16)	103 ± 16 (8)	122 ± 2.1 (16)
	ANOVA P	<0.025	<0.01	<0.05
	[a] ($P < 0.01$) compared to controls			
B. (i)	Control	100 ± 8 (8)	100 ± 14 (5)	128 ± 1.6 (8)
(ii)	Low Na	93 ± 18 (8)	106 ± 18 (5)	130 ± 0.8 (8)
(iii)	High Na	101 ± 22(7)	113 ± 18 (5)	128 ± 2.1 (7)
	ANOVA P	>0.05	>0.05	>0.05

Plasma from dehydrated rats was associated with a rise in plasma sodium, and an inhibitory effect on tubular Na-K-ATPase and rubidium transport (A.). By contrast, a high sodium diet had no effect on Na-K-ATPase or rubidium transport (B.). These results suggest that in terms of common homeostatic insults, the release of circulating inhibitors of Na-K-ATPase is more responsive to water deprivation than sodium largesse.

Acute filtration failure induced by p-aminophenol in rats is not dependent upon activation of tubulo-glomerular feedback. *P.J. Harris, M.A. Henry, L.L. Walker, S.L. Skinner, J.D. Tange, Departments of Physiology and Pathology, University of Melbourne, Melbourne, Australia.* Severe reduction of glomerular filtration rate is an essential initial feature of the acute renal failure that accompanies tubular necrosis. Obstructive casts within the tubule or the activation of tubulo-glomerular feedback in response to reduced proximal reabsorptive activity and consequent increased solute delivery to the distal tubule have been proposed as factors contributing to the low filtration rate. The p-aminophenol model in rats displays decreased glomerular filtration and a parallel increase in proximal and distal tubule hydrostatic pressure, but with little change in urine flow. This filtration failure occurs without evidence of cast formation. In further studies using this model, tubular fluid was collected under free–flow conditions from proximal or distal tubules in two groups of animals before and at intervals up to 180 minutes after single i.v. injections of p-aminophenol (300 mg/kg body wt). Proximal tubule pressures were measured prior to fluid collections.

	Group 1 ($N = 8$)		Group 2 ($N = 6$)	
	Prox Pressure, mm Hg	Prox Flow, nl/min	Prox Pressure	Distal Flow
Control	17.3 ± 2.2	19.8 ± 2.3	15.0 ± 0.5	3.7 ± 0.9
	$P < 0.001$	N.S.	$P < 0.001$	N.S.
pAP	41.3 ± 2.6	16.3 ± 1.7	34.8 ± 2.7	3.4 ± 0.6

Proximal tubule pressure more than doubled in both groups but with no significant changes in proximal or distal flow rates under free–flow conditions. Thus, glomerular filtration is reduced in this model as a

result of the increased tubular pressure rather than as a consequence of afferent arteriolar constriction. This conclusion is supported by the observation that renal blood flow is maintained while filtration rate falls and provides no evidence for activation of tubulo-glomerular feedback.

Prostaglandins and vasodepressor phsopholipids in the reversal of renal clip hypertension in the rat. *H.M. McGowan, R. Vandongen, J.P. Codde, K.D. Croft, University Department of Medicine, Royal Perth Hospital, Perth, 6000, Australia.* Previous studies have implicated vasodilatory PGs in the reversal of hypertension following unclipping the one–kidney, one–clip (1K,1C) hypertensive rat. The capacity of aorta to synthesize PGI_2 was compared in clipped (Group A, $N = 9$), unclipped (Group B, $N = 8$), and (Group D, $N = 9$), and sham–unclipped (Group C, $N = 9$) 1K,1C hypertensive rats. The opportunity was taken also to examine the possible involvement of PAF, a potent renal antihypertensive phospholipid, in the reversal of renal clip hypertension. This was assessed by bioassay of the precursor lyso-PAF in Group C & D, using ^{14}C-serotonin labelled platelets, following acetylation in vitro. Hypertensive rats (systolic BP > 180 mm Hg) were fed a linoleic acid supplemented diet for four weeks to enhance PG production to amplify the effects of unclipping on PG synthesis. After measuring BP, Group A was killed immediately whereas Group C was sham–unclipped, and Group B & D unclipped before killing 24 hours later. Blood was drawn for measurement of lyso-PAF and the aorta removed for determination of 6-keto $PGF_{1\alpha}$, the hydrolysis product of PGI_2. BP fell in the unclipped rats (Group B & D), but did not change in the sham–unclipped rats (Group C). Aortic 6-keto $PGF_{1\alpha}$ was increased in the unclipped groups (Group B, 15.4 ± 2.4 ng/mg; Group D, 10.8 ± 2 ng/mg) (mean ± SEM) compared with Group A (7.7 ± 1 ng/mg) and Group C (7.1 ± 1 ng/mg) ($H = 13.74$, $P < 0.01$). Lyso-PAF was also significantly increased in the unclipped (Group D, 2.62 ± 26 μg/ml) versus the sham–unclipped (2.11 ± 0.23 μg/ml) group ($P < 0.05$). These findings suggest enhanced phospholipase A_2 activity in the unclipped rat, increasing synthesis of aortic PGI_2 and PAF. These may be involved in the reversal of 1K, 1C hypertension.

The effect of blood pressure and dietary fat on prostaglandin synthesis in 1-kidney, 1-clip Goldblatt rats. *J.P. Codde, H.M. McGowan, R. Vandongen, L.J. Beilin, University Department of Medicine, Royal Perth Hospital, Perth, 6000, Australia.* It has been proposed that vasodilator prostaglandins (PG) play an important role in the regulation of blood pressure (BP). This study examines the effects of diets enriched with fatty acids on PG synthesis and blood pressure in 1-kidney, 1-clip Goldblatt rats. Rats with BP > 180 mm Hg within eight weeks of nephrectomy and renal artery stenosis were paired by weight and blood pressure, and placed on either a prostanoid 'enhancing' safflower oil (77% LA) or prostanoid 'inhibitory' cod liver oil/linseed oil mix (6.7% EPA, 4.8% LNA, 4.7% LA) enriched (10% wt/wt) diet for four weeks. At completion of the dietary period, a 24 hour urine sample was collected and then blood, aorta, and remaining kidney removed for lipid and PG analysis. Animals with BP < 150 were also paired and followed the same dietary and experimental protocol. Comparison between the two BP groups revealed that on both dietary regimens hyptertensive rats produced significantly more aortic 6-keto-$PGF_{1\alpha}$ and serum TXB_2. Rats on the EPA/LNA enriched diet had significantly impaired ability to generate serum TXB_2 (36%), aortic 6-keto-$PGF_{1\alpha}$ (65%), renal homogenate 6-keto-$PGF_{1\alpha}$ (64%) and PGE_2, and urinary 6-keto-$PGF_{1\alpha}$ excretion (52%) compared to LA enriched rats. Despite these differences in PG synthesizing capacity, dietary linoleic acid did not protect against nor did EPA/LNA exacerbate established 1-kidney, 1-clip hypertension. However the enhanced synthesis in vitro of aortic PGI_2 and blood TXB_2 in hypertensive rats appears to be an adaptive or pathological response to the high blood pressure.

Comparison of nicardipine and propranolol, added to hydrochlorothiazide, in the treatment of hypertension. *R.N. Wyndham, J. Shaw, R. Gordon, R.V. Jackson, G. Macdonald, G. Stokes, Repatriation Hospitals, Sydney and Brisbane, Prince Henry Hospital, and Royal North Shore Hospital, Sydney, Australia.* Nicardipine is a calcium channel blocker. We compared nicardipine, 30 mg tds (N) with propranolol, 40 mg tds (P) given to patients with moderate to severe hypertension treated with hydrochlorothiazide 50 mg daily (H). The study was a 14 week double–blind randomized crossover design. All patients took (H) for 14 weeks. During the first four weeks they also took a placebo. This was followed by two 4 week periods of active treatment separated by a two week washout. Twenty–four patients completed the study. Their ages ranged from 28 to 75 years and 20 were male. Results at the end of each four week period (mean ± SEM)

	H + Placebo	H + N	H + P
Supine BP, mmHg			
Systolic	159.1 ± 4.0	141.8 ± 3.1	140.5 ± 3.8
Diastolic	102.3 ± 1.6	87.4 ± 2.6	86.0 ± 2.0
Standard BP, mmHg			
Systolic	149.4 ± 3.9	135.9 ± 4.1	132.3 ± 3.4
Diastolic	102.8 ± 1.4	91.3 ± 2.6	89.4 ± 1.7
Pulse rate/min			
Supine	77.9 ± 1.9	83.1 ± 2.0	67.0 ± 1.8
Standing	83.2 ± 2.5	89.0 ± 2.4	67.9 ± 1.6

N and P had similar effects on blood pressure. However, P significantly reduced pulse rate compared to N ($P < 0.01$). Side effects were common; 23 patients reported 121 adverse effects: 48 mild, 50 moderate, and 23 severe. Of these 69 were ascribed to treatment: 10 to H + placebo, 32 to H + N and 17 to H + P. Nicardipine is as effective as propranolol when given with hydrochlorothiazide for moderate to severe hypertension, but is associated with more side effects.

An open study of enalapril in the treatment of hypertension. *R.N. Wyndham, M.L. Marel, J.R. Lawrence, J. Shaw, Repatriation General Hospital, Sydney, Australia.* Enalapril (E) is a new angiotensin converting enzyme inhibitor. We conducted an open, dose–finding study of E combined with hydrochlorothiazide (H) in patients with hypertension, supine diastolic BP (SDP) 95 to 120 mm Hg after two weeks on no treatment. All patients entered were started on E 10 mg/day and were reviewed fortnightly. If SDP had not fallen below 90 mm Hg, there was a stepwise increase of E by 10 mg daily to 40 mg daily and introduction of H 25 mg, then 50 mg per day. If SDP was still above 90 mm Hg, a third agent was added. Twenty patients were enrolled and 15 completed the study. Their ages ranged from 26 to 82 years and 14 were male. The doses of drug employed were (mean ± SD): E 26.7 ± 8.2 mg/day, H 23.3 ± 17.5 mg/day. Two patients required a third agent, 1 Verapamil 40 mg bd, 1 Prazosin 1 mg bd. Results (mean ± SEM):

	Baseline	E 20 mg/day	Final
Supine BP (mm Hg)			
Systolic	178.7 ± 5.4	161.7 ± 7.0	142.7 ± 3.9
Diastolic	104.9 ± 2.2	96.2 ± 3.0	83.3 ± 1.9
Standing BP (mm Hg)			
Systolic	171.0 ± 5.9	159.9 ± 6.0	138.8 ± 2.8
Diastolic	109.3 ± 2.0	100.6 ± 2.7	88.3 ± 2.0

Of the 20 patients enrolled, 15 reported a total of 26 side effects, of which 20 were thought to be due to therapy. Enalapril is an effective antihypertensive agent when used in combination with hydrochlorothiazide. It has a similar side effect profile to other agents.

Proteinuria of diabetes mellitus (DM) is prevented by phosphate depletion (PD). *D.C.H. Harris, A.C. Alfrey, R.W. Schrier, Department of Medicine, University of Colorado School of Medicine, Denver, Colorado, USA.* PD reduces the proteinuria and delays the progression of renal dysfunction in rats with nephrotoxic serum nephritis and partial nephrectomy. In the present study, the effect of PD on the proteinuria of DM was examined in Sprague–Dawley rats given streptozotocin (30 to 50 mg/kg i.v.) one week after right nephrectomy. One week later, rats were paired according to body weight, renal function and severity of DM. Rats were pair fed a normal rat diet, with (PD) or without (PR) the phosphate binder dihydroxyaluminum acetoacetate (DHAAA 15 g%). Blood glucose (BGC) was measured twice weekly, body weight weekly, and mean arterial pressure (MAP) and other metabolic parameters every two weeks. PD rats had lower serum (1.39 vs. 2.18 mmol/liter, week 11, $P < 0.001$) and urine (0.19 vs. 6.57 mmol/24 hr, week 11, $P <$

0.001) phosphate than PR rats. Serum Ca (2.79 vs. 2.38 mmol/liter, week 11, $P < 0.005$) and urine Ca (9.33 vs. 3.83 mmol/24 hr, week 11, $P < 0.001$) were higher in PD than PR rats. At three months, there was no significant difference between the two groups (PD vs. PR) in body weight (298 vs. 302 g), kidney weight (2.26 vs. 2.24 g), MAP (86.7 vs. 86.4 mm Hg asleep), urine output (103 vs. 109 ml/24 hr), BGC (20.8 vs. 21.1 mmol/liter), insulin requirements (10.4 vs. 10.9 U/week), serum creatinine (0.070 vs. 0.068 mmol/liter), creatinine clearance (3.66 vs. 3.77 ml/min/kg body wt) or serum albumin (30.1 vs. 29.3 g/liter). However, from week 3, proteinuria was significantly lower in PD rats; at three months 20.3 (PD) vs. 77.4 mg/24 hr (PR) ($P < .001$). PD alone, therefore, reduces the magnitude of proteinuria early in DM and remains protective for at least three months. This protective effect of PD is independent of other factors such as protein intake, serum albumin, severity of DM, MAP, and renal function.

Idiopathic membranous glomerulonephritis: 25 years experience with 144 cases. *B.F. Murphy, K.F. Fairley, P.S. Kincaid-Smith, The Royal Melbourne Hospital, Melbourne, Australia.* Clinical details of 144 patients (80 male, 64 female) with idiopathic membranous glomerulonephritis were reviewed. Median age at presentation was 37 (males 43, females 31, range 13 to 79). Duration of follow up was 1 to 280 months (median 51). Forty-five percent and 25% were followed for more than five and 10 years. Principal presenting symptom was edema (56%) and 54% (70% of males, 39% of females) had proteinuria >3.5 g/day. Median s. albumin was 26 g/liter and median p. creatinine was 90 μmol/liter (>120 μmol/liter in 18%). Microscopic hematuria was present in 32% and diastolic BP > 110 mm Hg in 24%. Renal venograms in 24 patients demonstrated thrombosis in 12. Associated diseases included: malignancy (3), sarcoidosis (2), Guillain-Barre syndrome (2), and reflux nephropathy (2). Forty-three percent of patients were treated at some stage with Cyclophosphamide, Dipyridamole and Warfarin. At conclusion of follow-up, 50% of patients were alive with normal renal function, eight patients (6%) (one female, seven males) had developed end-stage renal failure, 19 (13%) had impaired renal function, 15 (10%) had died from non-renal causes, and 30 (12%) were lost to follow-up. Thirty-eight percent of initially nephrotic patients remained nephrotic. Renal survival was 95% and 93% at five and 10 years; patient and renal survival was 89% and 82%. The 28 patients who suffered deterioration in renal function were 22 male and six female ($P < 0.05$) and had significantly lower median s. albumin, high median urinary protein and high median p. creatinine than the other patients at presentation. Median predicted (or actual) time for development of ESRF in the 21 patients with progressive deterioration was 7.3 years.

Outcome of patients with Henoch Schönlein nephritis. *R.J. Walker, R.R. Bailey, K.L. Lynn, C.P. Swainson, Department of Nephrology, Christchurch Hospital, Christchurch, Australia.* Glomerulonephritis (GN) is the main determinant of mortality in the Henoch Schönlein syndrome. Renal involvement occurs in 28 to 90% of those with the syndrome. Seventeen patients (10 males) with the Henoch Schönlein syndrome and GN who had a renal biopsy between 1 June 1973 and 31 May 1985 were studied prospectively. The patients were aged from 7 to 42 years (mean 20.4). Indications for renal biopsy were microscopic hematuria (six), macroscopic hematuria (six), acute nephritic syndrome (four), and nephrotic syndrome (one). The initial biopsy (ISKDC Classification) showed minimal change (four), mesangial proliferative GN (five), focal or diffuse proliferative GN with <50% crescents (six), diffuse proliferative GN with >50% crescents (one), and proliferative GN (one). Immunofluorescence for mesangial IgA was positive and electron microscopy showed characteristic electron dense deposits in all biopsies. Follow-up was from eight months to 9.5 years (median 41 months). No patients were treated with steroids or immunosuppressive agents. Hypertension was treated aggressively. Thirteen patients were alive with normal renal function, three reached end-stage renal failure and one was lost to follow-up. The five year cumulative renal survival rate was 90%. This was similar to other reports. A poorer prognosis was associated with a clinical presentation with either the acute nephritic or nephrotic syndrome and with crescent formation. Regular assessment for a minimum of five years is recommended for patients with Henoch Schönlein GN.

Adult Henoch-Schönlein Nephritis : A retrospective review. *R.J. Faull, D. Shaw, I. Aarons, A.J. Woodroffe, A.R. Clarkson, Renal Unit, Royal Adelaide Hospital, Adelaide, Australia.* Twenty-seven patients with Henoch-Schönlein Purpura had renal biopsies at the Royal Adelaide Hospital from June 1975 to September 1985. Details of initial presentation and follow-up were recorded, including severity of histological lesions of initial renal biopsies. Average follow-up was 28 months. All patients had microscopic hematuria at presentation, 26 had the characteristic purpuric rash, and 25 had proteinuria. At follow-up, four patients had died as a direct result of the disease and one was on chronic hemodialysis. Nineteen out of 25 patients followed had persistent detectable abnormality (hypertension, proteinuria and/or elevated plasma creatinine). Of these 25 patients, 10 presented in acute renal failure, and overall these had a poor outcome. Initial normal serum creatinine usually heralded few or no later abnormalities. Initial degree of proteinuria was unreliable as a prognostic marker. The glomerular lesions were rated on a scale of 1+ to 3+ for severity of histological lesions; the more severe had a correspondingly worse outlook. The presence of greater than 20% crescents on renal biopsy predicted poor outcome; however, lack of or small numbers of crescents was an unreliable indicator of favorable outcome. Treatment with plasmapheresis appeared to give a good response in the short term with four severely involved patients; however, one patient died and another eventually required chronic hemodialysis. Patients treated with high dose steroids generally had a poor outcome, probably reflecting their severe initial disease.

Hemodynamic and metabolic effects of oral hydrocortisone (F) administration in man. *J.A. Whitworth, J.M.C. Connell, A.F. Lever, R. Fraser, Department of Nephrology, Royal Melbourne Hospital, Melbourne, Australia, and MRC Blood Pressure Unit, Glasgow, Scotland, United Kingdom.* Steroid therapy is used widely in management of renal disease. However, although the features of iatrogenic Cushings's syndrome are well recognized, the hemodynamic and metabolic consequences of steroid administration have not been systematically examined. Six laboratory workers (age 24 to 48 years) on a diet with 150 mmol Na and 70 mmol K were given F 50 mg orally, 6 hourly for five days. P. cortisol rose from 11 ± 1 to 31 ± 2 μg/100 ml ($P < 0.01$). Systolic blood pressure rose from 116 ± 1 to 121 ± 4 mm Hg, $P < 0.01$, with no change in diastolic pressure. Pulse fell from 65 ± 2 to 58 ± 3 beats/min, $P < 0.05$. Body weight increased from 71.0 ± 2.1 to 72.0 ± 2.2 kg ($P < 0.001$). P. [Na] rose from 139 ± 1 to 141 ± 1 mmol/liter ($P < 0.01$) and p. [K] fell from 4.2 ± 0.1 to 3.7 ± 0.1 mmol/liter ($P < 0.001$). [Cl] and [HCO_3] were unchanged. P. urea fell from 5.7 ± 0.2 to 5.1 ± 0.5 mmol/liter ($P < 0.05$) and p. creatinine from 90 ± 3 to 77 ± 0.5 μmol/liter ($P < 0.05$). P. alkaline phosphatase fell from 69 ± 5 to 57 ± 4 i.u/liter ($P < 0.001$). The liver enzyme AST fell from 16 ± 1 to 12 ± 2 i.u/liter ($P < 0.01$), but there were no changes in ALT or γGT. P. albumin fell from 41 ± 1 to 36 ± 1 g/liter ($P < 0.001$). Total p. protein fell from 60 ± 1 to 54 ± 54 ± 1 g/liter ($P < 0.001$). Corrected p. calcium and p. phosphate were unchanged. Uric acid fell from 0.37 ± 0.02 to 0.24 ± 0.01 mmol/liter ($P < 0.02$). Urine volume was unchanged but there was a diuresis on F withdrawal, 1.35 ± 0.1 liter to 2.31 ± 0.24 liter, $P < 0.001$. There was initial urine sodium retention followed by a natriuresis on F withdrawal, 126 ± 8 mmol/day control, 60 ± 9 ($P < 0.01$) on day 1, 306 ± 25 mmol/liter post-F, ($P < 0.001$). Creatinine clearance was unchanged. Hemoglobin and hematocrit (42 ± 1 to 34 ± 1%, $P < 0.001$) fell. There was a rise in white cell count from 4.8 ± 0.3 to 7.1 ± 0.7/mm^3 ($P < 0.001$) and a fall in lymphocyte count from 31 ± 2 to 23 ± 2% ($P < 0.01$). Platelet count was unchanged. Plasma volume rose from 3.14 ± 0.08 to 3.9 ± 0.14 liter, ($P < 0.01$). These results indicate that oral steroid administration invariably produces substantial hemodynamic and metabolic perturbations.

Improved dietary management of children with chronic renal failure. *K.F. Jureidini, M.J. van Renen, L. Daniels, G.N. Hill, R.J. Hogg, T.R. Southwood, R. Vining, Renal, Dietetics, Pharmacy and Chemical Pathology Departments, Adelaide Children's Hospital, Adelaide, South Australia.* A strict low phosphate and protein diet with keto acid precursors of the essential amino acids and histidine was evaluated in 19 children with chronic renal failure. We monitored the effect on growth, well being, metabolism, bone disease and renal function. The study diet differed from conventional diet for chronic renal failure as below.

	Conventional diet	Study diet
Phosphate restriciton	Nil	Intense
Protein	2 g/Kg/day	1.2 g/Kg/day
Keto acid mixture	Nil	0.3 g/Kg/day

Keto acid precursors of the essential amino acids and histidine were given as a relatively palatable orange flavored drink (Sharp Laboratories) or a sugar–coated granule form (Ketoperlen - Pfrimmer). Both groups received bicarbonate to normalize serum levels, phosphate binding gels to normalize serum phosphate, and 1,25 DHCC to normalize serum alkaline phosphatase and keep serum calcium at the upper range of normal. Fourteen children on the study diet had previously been on conventional management for at least 12 months and acted as their own controls. Five had not previously been on any dietary management. Monitoring included both intact and mid-molecule parathyroid hormone (PTH) assays, growth measurements, activity and psychological acceptance, multiple biochemical analysis of blood and urine, bone assessment and serial GFR measurements. After 18 months, the diet continued to be generally well tolerated. Compared with the conventional diet, patients have continued to show significantly improved growth velocity, bone disease, general activity, fall in urea levels, reduced bicarbonate requirements, and normalization of PTH levels. GFR has not significantly changed after one year. Serum lipid studies have shown general improvement and marked improvement in those previously untreated. The study diet appears to be well tolerated with most indices significantly improved and no evidence of any deleterious effects.

Typing of glomerular mononuclear cells associated with glomerular rejection. *Y. Hiki, A.S.-Y. Leong, T.H. Matthew, A.E. Seymour, V. Pascoe, A.J. Woodroffe, Renal Units, Royal Adelaide, Queen Elizabeth Hospitals, and Division of Tissue Pathology, IMVS, Adelaide, South Australia.* To investigate the pathogenesis of glomerular transplant rejection (GTR), we have analyzed intraglomerular mononuclear cells from 20 biopsies with typical features of GTR (segmental or global occlusion of capillaires by swollen cells). These were compared with 10 biopsies showing cellular rejection but no glomerular pathology (CTR). Microwave fixation and an avidin–biotin immunoperoxidase technique were used with the following monoclonal antibodies; Leu1 & OKT3, Leu3a+b & OKT4, OKT8, OKB7, OKM1 and OKDR. The results (Table) showed a significant increase of T cells (leu1, OKT3), helper T cells (Leu3a+b, OKT4), cytotoxic T cells (OKT8) and monocytes (OKM1) in the patients with GTR compared with CTR patients (all $P < 0.001$, Mann–Whitney U test). Of the T cell subsets, cytotoxic T cells outnumbered helper T cells by a mean ratio of 3.2:1. These results suggest that T cells, predominantly of the cytotoxic subset, and monocytes are involved in the mediation of glomerular rejection.

	% Positive glomerular cells (mean ± SE)	
	GTR ($N = 20$)	CTR ($N = 10$)
T cells	3.7 ± 0.5[a]	0.4 ± 0.1
helper T cells	1.3 ± 0.2[a]	0.2 ± 0.1
cytotoxic T cells	3.2 ± 0.5[a]	0.2 ± 0.1
B cells	0.2 ± 0.1	0.1 ± 0.1
Monocytes	3.5 ± 0.6[a]	0.4 ± 0.1
DR positive cells	36.1 ± 2.2	30.1 ± 1.1

[a] $P < 0.001$

The risks of pregnancy in renal transplantation. *P.J. O'Connell, J.F. Mahony, R.J. Caterson, J.H. Stewart, The Departments of Renal Medicine, Sydney and Royal North Shore Hospitals, Sydney, N.S.W., Australia.* In a retrospective review of pregnancy in renal allograft recipients from 1974 to 1985, 11 women had 18 pregnancies. There were three surgical abortions, nine live births including one set of twins, five intra-uterine deaths (IUDS) and one miscarriage; one pregnancy is currently in its third trimester. The initial mean serum creatinine was 0.12 mmol/liter (range 0.08 to 0.20) and only two women had living donor grafts. Azathioprine and prednisolone were used for immunosuppression except in one case treated with Cyclosporin A and prednisolone. Twelve pregnancies in seven women had worsening of hypertension or developed hypertension during pregnancy. Proteinuria was present in 11 pregnancies. Seven pregnancies were associated with a deterioration in renal function; three were due to hydronephrosis, three to recurrent glomerulonephritis and one to rejection. Of nine live births, six were by vaginal delivery and three by cesarean section (including twins). Six were female and three male. The average gestation was 34.5 weeks and only one reached 38 weeks. The mean birth weight was 2027 g with four neonates small for gestational age. One male infant died at day three from intraventricular hemorrhage and hyaline membrane disease; there were no abnormalities in the remainder. Of the five IUDs, one was noted to have hydrocephalus, and three were small for gestational age. In conclusion, there is considerable risk to both mother and fetus in most cases. None of the pregnancies in this series were uncomplicated and the chance of a live baby was 64%.

Cefotaxime: It's use in CAPD associated peritonitis. *C.J. Wood, N.M. Thomson, R.C. Atkins, Department of Nephrology, Prince Henry's Hospital, Melbourne, Australia.* Continuous ambulatory peritoneal dialysis, (CAPD) is now accepted as a suitable treatment for patients with end–stage renal failure. The major complication, however, is the high incidence of peritonitis and effective, rapid treatment of these peritonitis episodes is important to minimize patient morbidity and perhaps, mortality. The initial choice of antibiotic should therefore effectively cover the major types of causative organisms. Cefotaxime, a new broad–spectrum cephalosporin with both gram–positive and entensive gram–negative cover should be very effective in the treatment of CAPD-associated peritonitis. Between December 1984 and August 1985 all CAPD patients with peritonitis at P.H.H. (Melb.) have received intraperitoneal Cefotaxime, 1 g as loading dose then 100 mg/liter as the primary antibiotic therapy. This antibiotic was continued for 14 days and changed only if it was apparent that the peritonitis episode was not improving or side effects occurred. Forty peritonitis episodes occurred in 29 patients during this time with clinical cure resulting in 27 of these episodes. Cefotaxime was discontinued on 13 occasions giving an overall failure rate of 33%. Although high, this is similar to our previous experience using other initial antibiotic regimes which has seen a 30 to 40% failure rate. The reasons for discontinuation include: resistant organisms (four multiple antibiotic resistant staphylococci, two gram negative bacilli, one Diphtheroid, one Acinetobacter), no clinical response despite invitro sensitivity of organisms (four episodes) and drug side effects (one episode). No relapse of peritonitis occurred following completion of intraperitoneal Cefotaxime. We conclude that the broad antibacterial spectrum of Cefotaxime conveys suitability as treatment of CAPD-associated peritonitis except in patients with cephalosporin resistant organisms and is a suitable first–line drug where the organism is not known.

The Redy sorbent system permits nutrient administration during hemodialysis. *E. Feinstein, P. Friedman, M. Roberts, S.S. Massry, Division of Nephrology, University of Southern California School of Medicine and Organon Teknika Corporation, Los Angeles, California, U.S.A.* Patients with acute and chronic renal failure frequently need parenteral nutrition. Addition of glucose and amino acids to hemodialysate allows efficient uptake of these nutrients by the patient. Using single pass hemodialysis required marked reduction (below 50 ml/min) in dialysate flow rate, resulting in low urea and creatinine clearances. The purpose of this study was to evaluate the Redy sorbent system as a means of nutrient administration. Standard hemodialysis was performed with bicarbonate dialysate. Duration of dialysis therapy was four hours with a 0.77 square meter hollow fiber dialyzer using blood and dialysate flow rates of 200 ml/min. Glucose was added to the dialysate at hourly intervals in amounts of 48 to 120 g (total of 192 to 384 g). All patients received regular insulin (one to three units/hour) by intravenous infusion. Varying amounts of glucose and insulin were used in order to give the maximum amount of glucose while minimizing intradialytic hyperglycemia and post-dialysis hypoglycemia. Forty g of essential and nonessential amino acids were infused into the venous drip chamber.

The results of five studies are as follows:					
Glucose added (g/hr)				Uptake of glucose/4 hr	
0′	1′	2′	3′	–0/0	G
48	48	48	48	42	81
96	96	0	0	52	99
120	96	0	0	53	114
120	120	0	0	45	107
120	96	96	72	60	229

The glucose clearance was 51 ± 10 ml/min (SD). All patients became hyperglycemic during therapy and hypoglycemic post-dialysis. These results demonstrate that addition of glucose to the dialysate in the sorbent hemodialysis system permits efficient administration of glucose. This represents 304 to 859 kilocalories per dialysis treatment. The post-dialysis hypoglycemic is probably due to inadequate control of intradialytic hyperglycemia.

The pharmacokinetics and pharmacodynamics of nifedipine in normal volunteers and in patients with stable renal failure. *R.A. Robson, R.R. Bailey, J.R. Sharman, E.J. Begg, Department of Nephrology, Christchurch Hospital, New Zealand.* The pharmacokinetics and pharmacodynamics of two formulations of nifedipine, 10 mg capsule and 20 mg slow release tablet, were studied in five healthy volunteers (3 males, 2 females), creatinine clearance (mean ± SD 2.2 ± 0.2 ml/s) and 10 patients with stable chronic renal failure, (5 males, 5 females), creatinine clearance (mean ± SD 0.27 ± 0.19 ml/s), not on dialysis. Plasma nifedipine concentrations were determined by a specific gas–liquid chromatographic method. The limit of sensitivity for the assay was 1 μg/liter. The results are detailed in the Table. There were no statistically significant differences between the volunteers and the renal failure patients for any of the calculated parameters for both formulations of nifedipine. The 20 mg tablet gave a profile in both groups of subjects of a sustained release preparation with a lower maximum concentration (Cmax) and a longer time for maximum concentrations (Tmax) to occur. Large inter-individual variations in the calculated data is consistent with the known variability in bioavailability due to first pass metabolism. The observed reduction in blood pressure was consistent with the pharmacokinetic data, with the maximum effect occuring at the Tmax for both formulations. The reduction in blood pressure was not statistically significant, but there was a compensatory increase in heart rate. In contrast the reduction in blood pressure in the renal failure patients was statistically significant and there was no compensatory increase in heart rate.

	10 mg capsule	20 mg tablet
Volunteers		
AUC (h · μg/liter)	115 ± 10	197 ± 67
Tmax (h)	0.5 ± 0.4	2.0 ± 0.5
Cmax (μg/liter)	54.9 ± 16.3	26.3 ± 5.9
Renal failure patients		
AUC (h · μg/liter)	160 ± 42	220 ± 54
Tmax (h)	1.5 ± 0.7	3.5 ± 0.58
Cmax (μg/liter)	30.5 ± 11.4	23.8 ± 4.1

Inhibition of enzymatic disposal of catecholamines in renal failure. *R. Vandonge, Lisa Davidson, L.J. Beilin, Anne Tunney, Department of Medicine, University of Western Australia and Royal Perth Hospital, Perth, Australia.* Plasma free and sulphate conjugated catecholamines (CA) are elevated in chronic renal failure (CRF), presumably due to impaired renal clearance. However, reduced metabolic inactivation via enzymatic pathways may also contribute. This study examines the hypothesis that enzymatic methylation is inhibited in CRF, resulting in increased concentration of free CA and the utilization of alternative inactivating pathways, including sulphation. Plasma free and sulphated noradrenaline (NA) and adrenaline (A) were measured by radioenzymatic assay using internal standards in six patients with CRF before and after hemodialysis. Free and conjugated NA (0.75 ± 0.42 and 7.2 ± 1.5 ng/ml, respectively) and A (0.06 ± 0.02 and 4.41 ± 1.42) were higher before dialysis than after (0.39 ± 0.12 and 3.6 ± 1.0 for NA; 0.037 ± 0.008 and 1.6 ± 0.6 for A). These levels are higher than normal free and conjugated NA (0.27 ± 0.01 and 0.95 ± 0.06, respectively) and A (0.05 ± 0.005 and 0.19 ± 0.015) (N=46). The percentage of total CA which is free was smaller in CRF (9.3 ± 2.4% for NA and 2.1 ± 0.3% for A) than in normal (23 ± 1% and 23 ± 2%) plasma. Compared with pooled normal plasma, ^{3}H-methylation of internal standard (100 pg) was consistently inhibited in CRF plasma by 21 ± 2.6% for NA and 15.4 ± 2.2% for A. Dialysis incompletely removed this inhibitory effect. These findings confirm an inhibitory effect of uremic plasma on enzymatic methylation, and therefore the inactivation of CA. The increase in sulphated CA, although largely due to impaired clearance, may also reflect enhanced conjugation in order to maintain adequate extra-neuronal disposal.

Surgical management of renovascular hypertension—a comparison between fibromuscular hyperplasia and atherosclerotic lesions: A 20 year study. *J. Horvath, W. Fischer, J. May, R. Waugh, A.G.R. Sheil, A. Eyres, D. Tiller, J. Johnson, G.G. Duggin, B. Hall, Department of Renal Medicine, Royal Prince Alfred Hospital, Camperdown NSW, Australia.* In a 20 year period, 142 patients had surgery for the management of renovascular hypertension. Forty–four patients had fibromuscular hyperplasia (FMH) and 98 patients had atherosclerosis (AS). At follow–up (FU) patient survival, blood pressure (BP), number of antihypertensive drugs (DR), and serum creatinine (S.Cr) was documented. The results are expressed as mean ± SD and significance is $P < 0.05$. At operation the patients with FMH were 34 ± 11 years old. Patient survival at 15 years was 91%. At FU 1 to 228 months (100 ± 6), there was a significant fall in BP (185/113 ± 35/21 vs. 134/84 ± 17/10 mm Hg), and a reduction in DR (2.6 ± 1.5 vs. 1.4 ± 1.2). Twenty–seven of the 44 patients were available for repeat RA. Five patients had graft occlusion, four had nephrectomy, and the other repaired. Two further patients had narrowing of the graft with no adverse effect on BP. Nine of the remaining 20 patients had progression of FMH and the level of BP in those 11 patients compared to patients with no change was not different. At operation the 98 patients with AS were 52 ± 11 years of age. Patient survival at 10 years was 51%. In 34 patients with a pre-operative S.Cr >200 μmol/liter there was only 16% survival in the comparable period. The pre-operative BP for the AS group was 195/117 ± 37/23 mm Hg and there was a significant reduction in BP (156/92 ± 30/18 mm Hg) and DR (3 ± 1.4 vs 2.2 ± 1.2) at the time of FU 1 to 240 months (mean 58 ± 40) following surgery, but there was no change in renal function for the group as a whole. Forty–six patients had repeat RA. There were 11 graft occlusions, three graft stenoses and progression of AS in 13 patients. The remaining 19 patients had no further abnormality on RA. There was no correlation between level of blood pressure, or renal function and RA finding at FU. Surgical management results in different outcomes for the two groups of patients. In trying to establish the natural history and the impact of treatment strategy these diseases should be considered separately.

Chronic progressive renal lesions induced by lithium. *R.G. Walker, P. Kincaid–Smith, Department of Nephrology, The Royal Melbourne Hospital, Parkville 3050, Victoria, Australia.* New Zealand white rabbits, eight fed lithium [50 to 250 mmol/liter of LiCl/kg food (Li)] and seven controls (C) had sequential open renal biopsies at 0, 1, 3, 6 and 12 months. Quantitated histological changes; interstitial fibrosis (IF), tubular atrophy (TA), cast formation (CA) (determined by point counting or digitization) and glomerular sclerosis (GS) (% sclerosed glomeruli) were more marked in Li compared with C from as early as one month (IF; $P < 0.02$, TA; $P < 0.05$, CA; $P < 0.05$); and up to 12 months (GS; $P < 0.05$). Distal tubular dilatation and microcyst formation (determined by digitization) was also marked in Li compared with C from as early as one month ($P < 0.05$). The degree of distal tubular dilatation and other changes of chronic focal interstitial nephropathy tended to progress with duration of lithium exposure. At 12 months particularly, numerous mitotic figures were observed in tubular cells lining segments of the distal nephron in Li and macroscopically, Li kidneys were pale and granular and exhibited microcysts. Impairment of glomerular filtration (raised blood urea; $P < 0.02$, and raised serum creatinine; $P < 0.05$); were late features (12 months) in Li animals.

Polyuria, although evident in Li at one month did not appear to progress with duration of lithium exposure. This study confirms that lithium induces chronic lesions in the rabbit kidney, identifies similarities with the lithium–induced histological features described in human kidneys, and also suggests a possible animal model for other "cystic" kidney diseases.

Urinary tract disease in aboriginal subjects in south Australia. *D.J. Pugsley, B. Grime, E. Butler, A.J. Esterman, Renal Unit, Queen Elizabeth Hospital, Adelaide, Aboriginal Health Organization of South Australia and Division of Epidemiology of the South Australian Health Commission, Australia.* Aboriginal subjects (3103) were surveyed for the presence of urinary tract disease (UTD), using a cluster analysis technique, in urban, rural, and traditional tribal areas of South Australia between 1982 and 1984. As defined by the presence of proteinuria and/or hematuria (1+ on dipstick—Ames Co.) 16% of all subjects had UTD. The prevalence of UTD rose with increasing body mass index and also, until the fifth decade, with increasing age. Six percent of all subjects had 2+ proteinuria on testing. Fifteen percent of all subjects with UTD were diabetic (overall prevalence of diabetes in this population = 6%) and 40% of all diabetics had evidence of UTD. Fourteen subjects (0.45%) had elevated blood levels of creatinine and urea giving a prevalance rate for renal failure of 1:215 (4,700 per million). Comparison with an estimated prevalence rate of renal failure in the South Australian population, suggests that renal failure is likely to occur ten times more frequently in the Aboriginal population.

Renal disease and familial IgA nephropathy in an aboriginal family. *P.J. O'Connell, L.S. Ibels, M. Harris, M.A. Thomas, Department of Renal Medicine, Royal North Shore Hospital, Sydney, N.S.W., Australia.* An Aboriginal family which was noted to have a high incidence of renal disease was investigated. Twenty–five of 76 members from four generations had hematuria on screening. From this group, 48 members (21 males, 27 females, age range two to 86 years) from the main family with renal disease were studied further. All had repeated urinalyses and blood pressures measured. Thirteen had serum creatinine and IgA estimations, 11 had intravenous pyelograms (IVP) and eight renal biopsies. Twenty–one had hematuria and four hematuria and proteinuria. Five had hypertension, one a raised serum creatinine, two elevated serum IgA levels and one cortical scarring on IVP. All those biopsied (6 males, 2 females) had hematuria, five proteinuria, four hypertension, and one a raised serum creatinine. Histological, electron microscopy and immunofluorescent (IF) features were consistent with IgA nephropathy in five, mild arterial changes consistent with hypertension and diabetes in one, arteriolar C3 disease in one and no IF was available in one. HLA typing was performed in 27 family members and there was no difference in antigen frequency in those with IgA nephropathy when compared to the rest of the family or those with no renal disease. $HLAB_{12}$ and B_{35} were not present, and $HLADR_4$ was present in one person with hematuria. This study suggests that the incidence of renal disease may be high in the Aboriginal community and that IgA nephropathy may be common in this group.

Acute and chronic potassium tolerance during long–term captopril therapy in rats. *M.J. Field, J.R. Lawrence, Department of Medicine, University of Sydney, Concord Hospital, N.S.W. 2139, Australia.* To determine the effects of chronic inhibition of angiotensin II (AII) synthesis on potassium homeostasis, we studied rats treated continuously for three weeks with captopril (100 mg/kg/day in drinking water). Animals were divided into three groups, each with a corresponding untreated control group. Rats in Group I were fed a normal diet, while Group II rats ate a KCl-supplemented diet (approximately 20 mmol K/day) for the duration of the study. Group III animals ate the normal diet, but were given an acute KCl load at the end of the three–week observation period, immediately prior to sacrifice. At this time, blood was taken from animals in all groups for determination of plasma concentrations of K and aldosterone (Aldo), and adrenal glands were obtained for light–microscopic measurement of zona glomerulosa (ZG) width. Results were: (means ± SEM, N = 5–7/group; con=Controls, cap = Captopril–treated).

Group	I (con)	I (cap)	II (con)
Plasma K (mM)	4.0 ± 0.1	4.2 ± 0.1	4.0 ± 0.2
Aldo (ng/dl)	7 ± 1	8 ± 2	20 ± 6
ZG width (μ)	56 ± 2	57 ± 2	81 ± 2[b]
Group	**II (cap)**	**III (con)**	**III (cap)**
Plasma K (mM)	4.1 ± 0.2	8.4 ± 0.4	8.4 ± 0.3
Aldo (ng/dl)	23 ± 7	74 ± 14	29 ± 3[a]
ZG width (μ)	77 ± 8	—	—

[a] $P < 0.02$, compared to III (con).
[b] $P < 0.001$, compared to I (con).

It is concluded: (*1*) hyperkalaemia is no more likely after an acute or chronic potassium load in captopril–treated animals than in controls, given normal renal function; (*2*) chronic captopril therapy does not reduce the circulating aldosterone level in animals on control or high-K diets, but does blunt the rise in Aldo induced by an acute K challenge; (*3*) chronic dietary K loading stimulates growth of the adrenal zona glomerulosa, while long–term suppression of AII synthesis with captopril does not alter ZG morphology.

Natriuretic actions of gut peptides. *K.A. Duggan, G.J. Macdonald, The Prince Henry Hospital, Sydney, Australia.* Intravenous infusions of vasoactive intestinal peptide (VIP) and cholecystokinin octapeptide (CCK-8) are natriuretic in the rabbit. As significant metabolism of these peptides occurs in the liver, their renal effects may be mediated by other compounds. To establish whether VIP and CCK-8 act directly on the kidney and to define the renal responses to them or their metabolites, we compared the natriuretic responses to VIP and CCK-8 (10^{-4}–100 pmol/kg/min) infused intravenously and directly into the renal artery of six conscious male rabbits. The order of peptide infused and its route of administration were randomized. Each dose of peptide was infused for 30 minutes, during which blood pressure was recorded and urine collected. Blood was sampled at the end of each perfusion to determine renal plasma flow (e.r.p.f.—I^{125} Hippuran clearance) and glomerular filtration rate (g.f.r.—endogenous creatinine clearance). Responses were assessed by linear regression testing against the logarithm of the dose of infused peptide. In these doses, VIP had significant effects on renal circulation without altering arterial pressure or pulse rate. A log dose–related fall in e.p.r.f. ($-r = 0.50$ $P < 0.01$) and increase in derived renal vascular resistance ($r = 0.29$ $P < 0.05$) occurred. Total sodium excretion did not rise significantly, but when corrected for the nonsignificant fall in g.f.r., a significant increase in fractional sodium excretion, from a control mean of 1.36 to 4.43 ($r = 0.45$ $P < 0.01$) occurred. CCK-8 infusions had no effect on arterial pressure or pulse rate, while causing a log dose–related fall in e.r.p.f. ($-r = 0.35$ $P < 0.05$) and a significant rise in g.f.r. ($r = 0.47$ $P < 0.05$). Total sodium excretion rose significantly from a control mean of 11.15 μmol/min to 40.60 mol/min ($r = 0.46$ $P < 0.05$). However after correcting for the increase in g.f.r. fractional sodium excretion did not increase significantly. It is concluded that both VIP and CCK-8 directly affect renal sodium excretion, VIP by acting upon renal tubules and CCK-8 by elevating g.f.r.

Protection of intracellular homeostasis: Evidence for compartmentalization of intracellular potassium. *W.R. Adam, A.P. Koretsky, M.W. Weiner, Renal Unit & University of Melbourne Department of Medicine, Heidelberg, Australia; Departments of Medicine and Radiology, University of California, San Francisco; and Department of Medicine, Veterans Administration Medical Center, San Francisco, California, U.S.A.* Following an acute K^+ load, transfer of the potassium to the intracellular space helps protect the extracellular $[K^+]$ and the resting transmembrane potential, at a possible cost of disturbing the intracellular environment. The use of both ^{39}K Nuclear Magnetic Resonance (NMR) and K^+ selective electrodes to measure K^+ activity and chronic K^+ loading (HK), as a physiological model which appears to increase sequestered K^+, has provided evidence for intracellular K^+ compartmentalization. In liver homogenates from control (C) and HK rats: (*a*) addition of RbCl (200 μmole/g) increases the NMR K^+ signal (μmole/g) more in HK rats (19.3 ± 3) than control (11 ± 2, $P < 0.01$) consistent with displacement of K^+, by Rb^+, from NMR invisible sites; (*b*) K^+ selective electrodes detect less K^+, as a proportion of total K^+, in HK

compared to C rats (17% or approximately 12 μmole/g, $P < 0.01$), consistent with the presence of a K^+ compartment not seen by the electrode. Acute K^+ loading (1 mmole) in vivo increases tissue K^+ in HK liver (7 ± 2 μmole/g) and muscle (9 ± 2 μmole/g) but there was no change in NMR K^+. By contrast, in control rats increases in muscle K^+ (12 ± 2 μmole/g), with K^+ loading, are associated with increases in NMR K^+ (15 ± 3 μmole/g). These results suggest that some 10 to 15% of intracellular K^+ is within a compartment and that chronic K^+ loading leads to an increased capacity of this site. Sequestration of K^+ into this compartment may provide protection from changes in intracellular $[K^+]$.

A cortical gradient in glomerular angiotensin II receptors and their regulation during altered dietary NaCl intake. *F.A.O. Mendelsohn, A. Allen, R. Figdor, University of Melbourne, Department of Medicine, Austin Hospital, Heidleberg, Victoria, 3084, Australia.* Nephrons arising from superficial glomeruli differ in function and morphology from deeper, juxtamedullary nephrons. Also juxtaglomerular renin content and glomerular vasoreactivity to angiotensin II (AII) show a cortical gradient, being highest in superficial glomeruli. Using the technique of quantitative in vitro autoradiography, we have investigated the regional distribution of glomerular angiotensin II receptors (AIIR) and assessed the responses of glomerular and medullary receptors to altered dietary NaCl intake. Frozen sections (20 μm) of kidney from Sprague–Dawley rats were thaw-mounted onto coated slides, incubated with ^{125}I-[Sar^1]-AII to label AIIR, exposed to x-ray film and quantitated by computerized scanning densitometry. A very high density of AIIR binding was seen over glomeruli and vasa recta bundles and a moderate density occurred over the interbundle zone of the outer stripe. A highly significant gradient in glomerular AIIR was seen: on high salt intake, AIIR density was 207 ± 7 dpm/mm^2 in superficial glomeruli and 183 ± 5 in deep glomeruli ($P < 0.005$); this pattern was preserved during five days of low salt intake being, 185 ± 5 dpm/mm^2 in superficial glomeruli and 165 ± 5 in deep glomeruli ($P < 0.02$). Both superficial and deep glomeruli showed significant down-regulation of AIIR during low salt intake ($P < 0.02$ and $P < 0.05$, respectively) at a time when circulating and intrarenal AII level were elevated. These data reveal a significant gradient of glomerular AIIR. Receptors in both superficial and deep glomeruli down-regulate during low NaCl intake as do the more abundant AII receptors associated with vasa recta bundles.

Ischemic acute renal failure (ARF) is worsened by phosphate depletion (PD) but not by hypercalcemia (HC). *D.C.H. Harris, T.J. Burke, R.W. Schrier, Department of Medicine, University of Colorado School of Medicine, Denver, Colorado, USA.* PD worsens the severity of both the functional injury and the impairment in mitochondrial (Mito) respiration which attend ischemic ARF. Because PD, induced with the phosphate (P_i) binder dihydroxyaluminum aminoacetate (DHAAA, 15 g%), is also associated with HC, the present study examined the effect on ischemic ARF of HC alone achieved by adding dihydrotachysterol (D, 4.25 mg/kg diet) to the food of rats who were pair fed with controls (C). After 10 days both renal arteries and veins were clamped for 50 minutes; rats were sacrificed 24 hours later. Serum P_i (mmol/liter) was lower in DHAAA (1.25) than D (2.25, $P < 0.001$) and C (2.12, $P < 0.001$), and P_i excretion (mmol/24 hr) was higher in D (6.80) than DHAAA (0.13, $P < 0.001$) and C (2.55, $P < 0.001$). Prior to ischemia, D rats had greater HC (3.39 mmol/liter) than DHAAA (2.75 mmol/liter, $P < 0.001$) and C (2.53 mmol/liter $P < 0.001$), and greater tissue and Mito Ca, yet Ca excretion (mmol/24 hr) was higher in DHAAA (6.90) than D (3.73, $P < 0.005$) and C (0.19, $P < 0.001$). Twenty-four hours after clamping, serum creatinine (mmol/liter) was lower in D (0.249, $P < 0.005$) and C (0.270, $P < 0.05$) than DHAAA (0.357) and CCr (μl/min) was higher in both D (109, $P < 0.05$) and C (111, $P < 0.05$) than DHAAA (7.76). State 3 (S_3), State 4 (S_4) and uncoupled (FCCP) respiration fell to a greater extent in DHAAA (S_3 47%, S_4 39%, FCCP 49%) than D (S_3 27%, $P < 0.05$; S_4 17%, $P < 0.02$; FCCP 27%, $P < 0.02$) and C (S_3 19%, S_4 11%, FCCP 16%, $P < 0.005$) rats. The increase in tissue and Mito Ca after ischemia was similar in D and DHAAA rats. These results suggest that the detrimental effect of PD on ischemic ARF is independent of concomitant HC, and that the tissue and Mito Ca accumulation may be an epiphenomenon in this model.

Phosphate restriction prevents the concentrating defect of hypercalcemia (HC). *D.C.H. Harris, P.A. Gabow, R.W. Schrier, Department of Medicine, University of Colorado School of Medicine, Denver, Colorado, USA.* The concentrating defect of HC is well recognized, but the mechanism is unknown. To examine the mechanism of this concentrating defect in HC, the effect of HC alone was compared to that of HC which accompanies phosphate restriction. Three groups of rats ($N = 18$ each) were pair fed a normal phosphorus diet with (DHT) or without (control) the addition of dihydrotachysterol (5.25 mg/kg diet) or an otherwise identical low phosphorus diet without DHT (PD). After 10 days of diet, serum inorganic phosphorus was lower in PD (1.23 mmol/liter, $P < 0.001$) than in DHT (2.30 mmol/liter) or control (2.05 mmol/liter) rats. Weight loss was similar in the three groups, as was osmolar excretion in control (34.12 mOsm/24 hr), PD (35.71 mOsm/24 hr) and DHT (32.37 mOsm/24 hr) rats. In addition, serum Ca^{2+} was higher than control (2.61 mmol/liter) in both PD (2.96 mmol/liter) and DHT (3.02 mmol/liter) rats, both $P < 0.001$. Despite the similar degree of HC in PD and DHT rats, maximal Uosm after 24 hours of dehydration was lower only in DHT (2441 mOsm/kg, $P < 0.001$), compared to PD (3332 mOsm/kg) and control (3263 mOsm/kg) rats. Polydipsia and diuresis were greater in DHT (41.8 and 28.1 ml/day, respectively, $P < 0.05$) than in PD (34.2 and 20.1 ml/day) and control (32.4 and 18.1 ml/day) rats. Moreover, urinary Ca^{2+} excretion was higher in PD (8.88 mmol/day, $P < 0.05$) than in DHT (4.93 mmol/day) or control (3.37 mmol/day) rats, and tissue Ca content was greater in DHT (7.96 mmol/mg dry wt, $P < 0.005$) than in control (5.28 nmol/mg dry wt) and PD (5.87 nmol/mg dry wt) rats. In conclusion, phosphate restriction prevents the concentrating defect of HC. This protective effect may be mediated by the hypercalciuria of phosphate restriction and accompanying decrease in tissue Ca accumulation.

Hydrocarbon exposure, renal disease and membranous glomerulopathy. *R.S. Nanra, Department of Nephrology, Royal Newcastle Hospital, Newcastle, NSW, Australia.* Hydrocarbon [HC] exposure was assessed in 90 patients with renal disease (membranous glomerulopathy [MG] $N = 24$, glomerulonephritis [GN] $N = 40$, analgesic nephropathy [AN] $N = 15$, polycystic kidney disease [PCK] $N = 11$) and 16 controls by measurement of blood HC levels. Only 45.4% of PCK patients had DDT, and 36.4% had hexachlorobenzene [HCB] exposure compared to 66.7 to 95.8% of MG, GN and AN patients, and 75 and 87.5% of controls ($P < 0.005$). Dieldrin [DLD] was found only in patients with MG (33.5%) ($P < 0.0005$) and GN (5%). Except for 1 MG patient with a blood DLD level of 61 ppb, all remaining patients and controls had HC blood levels below the maximum recommended level (50 ppb). More patients with MG and DLD had microscopic hematuria (6 of 8 patients, $P < 0.05$) and an industrial occupation (5 of 8 patients, $P < 0.025$) than MG patients without DLD. Only 1 of 8 MG patients with DLD had a reduced GFR compared to 10 of 16 patients without DLD ($P < 0.1 > 0.05$). Conclusions: *(1)* there is a significant association between DLD exposure and MG, *(2)* microscopic hematuria is common in MG with DLD exposure, and *(3)* HCs are more commonly found in patients with acquired renal disease than in PCK disease.

Urinary nitrite in symptomatic and asymptomatic urinary infections. *H.R. Powell, Royal Children's Hospital, Melbourne, Australia.* The dipstick test for urinary nitrite is negative in 40 to 50% of symptomatic urinary infections. However, the impression was gained that the test may be more reliable in asymptomatic patients attending a follow-up clinic. The nitrite test was positive in 83 of 100 outpatients with asymptomatic urinary infection attending a follow-up clinic because of known predisposition to urinary infection. These patients had $\geq 10^5$ bacteria/ml in midstream urine specimens. In contrast, only 104 (52%) of 200 symptomatic patients with urinary infection attending an Emergency Department had a positive nitrite test. The difference was highly significant ($P < 0.0001$). By addition of a broth culture of E. coli to sterile urine it was found that four to six hours incubation at 37°C was required before the nitrite test became positive. This suggests that frequency of micturition in urinary infection reduces the reliability of the nitrite test. However, the higher sensitivity of the test in asymptomatic patients, together with its high specificity, suggests its suitability for regular home testing of patients with known predisposition to urinary infection with the aim of detecting and treating infections before symptoms arise. Weekly home tests appear most suitable.

Diabetic end–stage renal failure (ESRF): 11 years experience. *T.J. Thompson, Renal Unit, Wellington Hospital, Wellington, New Zealand.* Over the last 11 years, diabetic patients have formed an increasing proportion of new patients entering the Wellington Hospital dialysis and transplantation program. Over the last three years they averaged 27% of new patients. Between 1.1.75 and 31.12.85, 47 of 67 patients referred were accepted for treatment. There were 30 Europeans (64%) with a mean age of 45 years. Seventy–seven percent had type I diabetes. There were 16 Maoris (34%) with a mean age of 51 years. Eighty–one percent had type II diabetes. At the time of presentation all patients had retinopathy, ten patients were blind and a further 27 had received photocoagulation. There was clinical evidence of ischemic heart disease in 14 patients and 27 had peripheral vascular disease. Forty patients were hypertensive and 32 had neuropathy. The initial treatment was CAPD in 38 patients (81%), home hemodialysis (HH) in five patients, hospital hemodialysis in three patients and live related transplant in one patient. At completion of training 32% of patients resumed full–time work and 38% part–time. There have been 22 deaths. Patient survival for CAPD was 45% at four years (51% for non-diabetics [ND]. The four year patient survival for HH was 20% (80% for ND). For transplantation (12 patients) patient survival was 24% at four years (81% for ND). Graft survival was 36% at three years (59% for ND) but zero at four years. Despite a poorer overall survival compared to non-diabetics, treatment of diabetic patients has in many cases proved rewarding. The high proportion of Maoris (10% of the population) reflects a higher prevalence of type II diabetes.

Lupus nephritis: Clinical and pathological correlation. *B. Leaker, K.F. Fairley, J. Dowling, P. Kincaid–Smith, Department of Nephrology, The Royal Melbourne Hospital, Parkville, 3050, Victoria, Australia.* The clinical course of 135 patients with lupus nephritis was examined long–term as part of a prospective study. Biopsies were classified according to modified WHO criteria and showed 17% of patients had mild mesangial lesions, 10% focal lesions, 21% mild diffuse proliferative lesions, 37% severe diffuse proliferative lesions and 15% membranous lesions. Overall patient survival of 83% and 65% at five and 10 years, respectively, from onset of nephritis was similar to other recently published series. In contrast to the latter, the severe proliferative group had a significantly worse outcome than the other histological groups ($P < 0.01$) and only patients in this group progressed to end–stage renal failure. Hematuria was more common ($P < 0.05$) in the severe group and there was a striking correlation between histologic activity and urinary renal cell count ($r = 0.74$, $P < 0.001$). There was no correlation between serum creatinine, proteinuria or chronic lesions with urinary red cell count. In contrast to a previous study, there was no correlation between the presence of hyaline thrombi on initial biopsy and subsequent development of glomerular sclerosis. Although the value of renal biopsy has been questioned, we suggest that it remains a most important investigation in the management of lupus nephritis. Determination of urinary red cell count provides a most useful monitor of disease activity and response to treatment.

The effect of eicosapentanoic acid on active lupus nephritis. *B. Leaker, R. Quist, N. Salehi, P. Kincaid–Smith, Department of Nephrology, Nuclear Medicine, The Royal Melbourne Hospital, Parkville, 3050, Victoria, Australia.* Eicosapentanoic acid (EPA), a naturally occurring fatty acid, has been used in the treatment of atherosclerosis and renal disease. We have examined the effect of dietary EPA on the course of lupus nephritis in a historically controlled trial. Ten female patients, median age 29, with a diagnosis of SLE showed either diffuse proliferative or focal lesions on renal biopsy. All had persistent active urinary sediment despite conventional steroid and immunosuppressive therapy. In our experience, quantitative urinary red cell counts (Urbc) provide the most reliable non-invasive indicator of renal histological activity. All patients showed mean Urbc counts >50,000 rbc/ml measured on at least three occasions at monthly intervals prior to the start of the trial. Patients were treated with 3.2 g of EPA in addition to previous therapy. Seven of 10 patients showed a significant reduction in mean Urbc from median 143,000 (50 to 600,000) to 20,000 (8,000 to 400,000), $P < 0.01$. Three patients did not respond, one of whom was non-compliant. There was no change in proteinuria, GFR measured by ^{cr}EDTA clearance fell significantly with treatment from median 89(44 to 121) to 77(39 to 98) ml/min/1.73 m^2, $P < 0.01$. After stopping EPA therapy GFR rose to median 84(37 to 109), although the difference failed to achieve significance. Triglyceride levels fell significantly on treatment median 1.42(0.76 to 2.56) to median 1.19(0.5 to 1.81mmol/liter, $P < 0.01$. Four patients had decreased platelet survival median 5.35(3.4 to 5.6) measured by In^{111} oxine labelling method which returned to normal (8 to 10 days) on treatment. EPA may be a useful adjunctive therapy in the treatment of lupus nephritis, but may require regular monitoring of GFR.

Nephrocalcinosis and urinary tract anomalies in premature infants. *N.F. Woolfield, R.R. Haslam, G. LeQuesne, K.F. Jureidini, Renal and Ultrasound Units, Adelaide Children's Hospital, and Neonatal Intensive Care Unit, Queen Victoria Hospital, Adelaide, South Australia.* The incidence of nephrocalcinosis and urinary tract anomalies in premature infants (birth weight < 1500 g) was assessed. In their twelfth month of life, an ultrasound examination of the urinary tract was performed. Urine was collected at the same time and analysed for electrolytes, creatinine, osmolality, pH and B_2 microglobulin. Urine microscopy was also performed. Retrospective analysis of case records was made to assess factors of importance in the etiology of nephrocalcinosis. A total of 36 infants had ultrasounds performed. Three infants were found to have nephrocalcinosis. All had been on long–term frusemide for bronchopulmonary dysplasia. None had renal calculi present. Urinary microscopy, electrolyte and B_2 microglobulin showed no consistent differences compared to other infants in the study without nephrocalcinosis. Five other children had urinary tract anomalies. While two of these had uncomplicated duplications of collecting systems, the other three had major anomalies. One had a duplication of the collecting system with a ureterocoele. Another had bilateral pelviureteric junction obstruction, and a third had a shrunken kidney on the left with a dilated ureter on that side. A micturating cystourethrogram confirmed vesico-ureteric reflux. Conclusions: three infants of this population of premature infants had nephrocalcinosis, presumably due to long–term frusemide therapy. It had no effect on renal function as measured by urine electrolytes or B_2 microglobulin. Five others had urinary tract anomalies. While two were uncomplicated, the other three represent major anomalies, an incidence of eight per cent. A case can be made for the ultrasound examination of urinary tracts of all premature low birth weight infants.

Raised IgA anti-pneumococcal antibodies in IgA nephropathy (IgA GN). *P.A. Drew, W.N. Nieuwhof, A.R. Clarkson, and A.J. Woodroffe, Department of Surgery and Renal Unit, Royal Adelaide Hospital, South Australia and The State Health Laboratory, Queen Elizabeth II Medical Centre, Western Australia.* A postulated cause of IgA GN is the overproduction of IgA polymers and complexes in response to antigens presented to mucosal surfaces. To test this, we have measured the concentration of specific antibody to pneumococcal polysaccharides derived from common respiratory commensals and/or pathogens. Sera from 35 patients with IgA GN, six with SLE, eight with MGN and six with anti-GBM GN, and from 20 controls (C) were assayed. The concentrations of IgG and IgA specific for each of five pneumococcal polysaccharides (serotypes 2, 7F, 9N, 14 and 23F) were determined by ELISA. The results from the SLE, MGN and anti-GBM GN patients, being similar, were pooled and used as a patient control group (PC). Groups were compared using the Wilcoxon test or the Chi square test and differences were considered significant when $P < 0.05$. There was no difference in the concentration of IgG antibody for any of the serotypes between IgA GN and C, but the PC group had significantly lower concentrations than either IgA GN or C. In contrast, there was no significant difference between the PC group and C in the concentration of IgA antibody to four of the serotypes, but the concentration of IgA was significantly increased in IgA GN compared to both groups. (There was insufficient IgA antibody to serotype 2 to detect in the assay system used.) We conclude that IgA GN patients have significantly elevated concentrations of IgA, but not IgG, to common respiratory tract bacteria compared to normal controls or patients with other forms of nephritis.

Lead intoxication on the Sydney Harbour Bridge. *L.S. Ibels, C.A. Pollock, Department of Renal Medicine, Royal North Shore Hospital,*

St. Leonards, N.S.W., Australia. Lead intoxication is far more prevalent than recognized in those exposed to lead fumes and dust in industry. The early symptoms of lead intoxication are subtle and non-specific. Blood lead levels are a poor reflection of total body lead stores and potential toxicity but are frequently used as the only screening test of lead intoxication. Calcium EDTA chelation testing is a more sensitive test to detect total body lead stores. We report six cases of men employed on the Sydney Harbour Bridge with significant lead intoxication, all of whom have symptomatically benefitted from calcium EDTA chelation therapy. The bridge workers were involved with removal of lead based paint from Harbour Bridge for between six to twenty–eight years. Symptoms compatible with lead intoxication had been present for several years at the time of their first screening with a blood lead level in 1985. An EDTA chelation test showed a high lead load in all patients. Two had significant renal disease with chronic interstitial fibrosis on renal biopsy. EDTA chelation therapy in all six patients resulted in considerable symptomatic improvement. It is apparent that screening in the industrially exposed must be undertaken on a regular basis and the diagnosis of lead poisoning must be considered if considerable morbidity is to be avoided.

Acute renal failure due to focal necrotizing glomerulonephritis in a patient with non-Hodgkin's lymphoma: Resolution with treatment of lymphoma. *L.S. Ibels, C.A. Pollock, J.A. Levi, R.P. Eckstein, P. Wakeford, Department of Renal Medicine, Royal North Shore Hospital, St. Leonards, N.S.W., Australia.* Renal involvement in patients with lymphoma is more prevalent than generally recognized. Glomerulonephritis may occur in patients with lymphoma as a paraneoplastic phenomenon. In Hodgkin's disease, the most prevalent form of glomerulonephritis is minimal change glomerulonephritis, although proliferative, crescentic, membranous and focal sclerosing forms have been described. In non-Hodgkin's lymphoma, glomerulonephritis is less prevalent and minimal change glomerulonephritis is infrequently seen. We describe a patient with non-Hodgkin's lymphoma and acute renal failure (urea 14.3, creatinine 0.31 mmol/liter) due to focal necrotizing glomerulonephritis. Treatment of the lymphoma alone with Cyclophosphamide, Adriamycin, Vincristine, and Prednisone resulted in complete resolution of his lymphoma and return to normal of his creatinine clearance, urine protein excretion and biochemistry. His renal biopsy prior to initiation of treatment showed a focal necrotizing glomerulonephritis. Following induction of remission of his lymphoma, renal biopsy showed only mild mesangial hyperplasia. In summary, focal necrotizing glomerulonephritis, a relatively uncommon form of nephritis, may occur in association with lymphoma and resolve on induction of remission of lymphoma.