Abstracts

Rhythms of urine excretion in renal failure. P Hiller, R. Cove-Smith and M. S. Knapp, City Hospital, Nottingham. The circadian rhythms of many physiological functions, including urine excretion have previously been documented in healthy subjects. Abnormal rhythms have been described in a variety of disorders. Menzel (1962) reported abnormal rhythms of urine excretion in patients with renal failure, but his report lacks detail, especially relating to the clinical condition of the patients studied. Patients known to have renal failure and to be in a stable clinical state have been studied. Simultaneously, two healthy control subjects (matched for sex and age) were studied using the same techniques. Subjects were trained to record data on temperature, blood pressure, pulse rate and urine volume. Over a period of days, they made records and also saved aliquots of all urines passed. These urine specimens were later analyzed. The control subjects had normal rhythms. Seven of eight patients in renal failure demonstrated an increased nocturnal and a decreased daytime excretion of total solute, sodium and water. Potassium excretion remained maximal in the daytime. Studies in some patients indicate that the abnormal pattern of excretion may relate to an abnormal response to the recumbent posture, rather than to a reversal of an intrinsic circadian rhythm. The magnitude of these variations of excretion (greater than 100%) despite severe renal impairment, and the possible mechanisms involved, are of interest. The results suggest that large percentage changes in glomerular filtration rate may occur.

Acute reversible renal failure in patients with acute cholecystitis and cholangitis. R. P. Burden, J. G. Gray and G. M. Aber. Wessex Regional Renal Unit, St. Mary's General Hospital, Portsmouth, and Renal Research Laboratory, North Staffordshire Medical Institute, Stoke-on-Trent, England. Acute renal failure is a well-known complication of several extrahepatic biliary tract disorders including biliary tract surgery in the presence of obstructive jaundice, but there is little information regarding acute renal failure in otherwise uncomplicated acute cholecystitis. Renal function was measured serially in 14 patients with acute cholecystitis and in 2 with acute cholangitis. Whereas in six patients there was no evidence of renal impairment, four had modest elevations of plasma urea and creatine concentrations and six had acute renal failure of whom three required peritoneal dialysis. Renal function returned to normal. There was evidence of intravascular coagulation in all patients with renal failure. Only one patient who developed acute renal failure was hypovolemic, another had a positive blood culture and two had pancreatitis. It is suggested that the renal changes were a result of intravascular coagulation, itself secondary to various factors, demonstrated an increase in IgA levels. No explanation can yet be drawn for these abnormalities.

Lymphokine "skin reactive factor" (SRF) in lymphocyte culture supernatants from patients with nephrotic syndrome (NS). G. LaGrue, A. Branellec, S. Kheneumont, G. Hirbec and B. Weill. Department of Nephrology, Hôpital Henri-Mondor, INSERM et Association Claude Bernard, Creteil, France. In patients with the nephrotic syndrome (NS), the role of an increased capillary permeability is suggested by biological data and clinically by the prompt recurrence of proteinuria in some patients after transplantation. We have investigated the presence of "skin reactive factor" (SRF) in lymphocyte culture supernatants from these patients, for SRF is an enhancing vascular permeability factor. The lymphocyte culture was composed of 10^7 lymphocytes/ml in Medium 199 (80%) plus human normal serum (HNS) AB+ (20%), or in MEM Eagle. The reaction was stimulated with PHA-M Difco or concanavaline A (5 µg/ml). Supernatants were taken off on the third day; 0.1 ml of supernatant was injected intradermally to Hartley guinea pigs. Vascular permeability (immediate reaction) was determined by the Evans Blue technique; and measurement of the blue areas, after the guinea pig was killed, was performed 30 min after injection. Delayed reaction was studied by the evaluation of the cutaneous inflammatory process during a 24-hr period (erythema, induration), and by histological study at 24 hr. Immediate reactions (vascular permeability). No vascular permeability enhancing activity was found in control supernatants (medium alone, medium + HNS, +concanavaline or PHA). In supernatants from 23 normal subjects, the reactions were positive only in 4 individuals with a mean area of 50 ± 71 mm^2. Supernatants from 46 patients with NS gave strongly positive results in 40 cases (area> 50 mm^2). In relation to histological types of NS, the results are as follows (blue area): NS with minimal optical changes, 161 ± 80 mm^2; NS with membranoproliferative GN, 174 ± 103 mm^2; and control subjects, 50 ± 71 mm^2. Difference is highly significant between each group and controls. Delayed reactions. For this study, PHA-stimulated supernatants were not used for they may give positive results. Supernatants positive with the blue method always gave delayed positive results: erythema from the 2nd to 4th hr; then, induration maximum from the 12th to 15th hr, which disappeared after 24 hr, with area, 20 to 50 mm^2. Histologic findings show mixed type infiltration with morphoepithelial (some basophiles) and mononuclear cells. Negative supernatants with blue technique and control supernatants give negative delayed results. Pharmacological findings. The action of some inhibitors and activators was studied and compared to results obtained in guinea pigs for SRF. There was no inhibition of immediate reaction with antihistamine, antiserotonin, indomethacin or salicylate; meclofenamate and pyridine carboxylic acid inhibited the reaction. Enhancement of the reaction was observed with diethylthiodithiocarbamate (DTTC) and with the addition of HNS to MEM supernatants. Physicochemical findings. Biological activity disappeared by heating at 100°C, and was reduced 50% by heating 30 min at 56°C. It was not dialyzable, and could be precipitated by 66% ammonium sulfate. It was destroyed by pepsin and not modified by desoxyribonuclease. By Sephadex G 200 chromatography, activity was found in the fourth fraction, which in immunoelectrophoresis migrated with the albumin fraction. In summary, lymphocyte culture supernatants from patients with the NS contain SRF with an enhancing vascular permeability and proinflammatory effect; this factor is not present in normal subjects and in control supernatants. Pharmacological and biological properties of this factor are similar to guinea pig SRF. Modifications observed with meclofenamate, DTTC and addition of NHS suggest that it could be an activator of the kinin system. Physicochemical findings show that it is a protein migrating as albumin. To date, the lymphokines have been studied in animals but seldom in humans. Our results show that in humans, variations in lymphokine production may be present. Pathogenic implications are now under study.
and although emergency biliary tract surgery has been advocated for acute biliary tract diseases complicated by renal failure, the return to normal renal function in the present study favorably indicates conservative management.

The urinary excretion of IgM, IgG and C3 related materials FDP and sheep hemagglutinins in proliferative glomerulonephritis and following renal transplantation. J. L. Anderton, M. S. Hoq, M. Cunningham, J. M. Borowczyk, J. S. Robson and J. D. Cash. Western General Hospital. The urinary concentration of material related to complement (C3) IgM and IgG was measured along with fibrin/fibrinogen degradation products (FDP) and heterophile (sheep) hemagglutinins (SHA) in 15 patients with proliferative glomerulonephritis and 10 patients after renal transplantation. There was a significant correlation between both the FDP and SHA content and the concentrations of IgM, IgG and C3 related materials. However, detailed serial studies in patients with proliferative glomerulonephritis revealed that not all urine specimens with a high content of IgM, IgG and C3 related materials had a high concentration of FDP or SHA, or both. Investigations on the ten renal transplant patients confirmed previous reports that urine FDP and SHA estimations provided parallel information on the detection of rejection. Significant patients in the excretion of IgM, IgG and C3 related materials were observed in all patients. The responses to oral administration of indomethacin were studied in ten patients with proliferative glomerulonephritis and 10 patients after renal transplantation. There was an improvement in renal function. In the remaining six patients there was no fall in most of the urinary components, and this was associated with deterioration in renal function.

Immunity to kidney-derived antigen in human and experimental renal transplantation. R. J. Williams, Karen Eyres, N. P. Mallick, W. McN. Orr, G. Taylor and G. Williams. Renal Transplantation Unit, Manchester Royal Infirmary and University of Manchester, Manchester, England. In order to extend our previous studies using the leucocyte migration test (LMT) of immunity to a kidney-derived antigen in glomerular disease and renal transplantation, we have developed a model using paired, unrelated dogs. Five pairs of animals have now been studied. All animals were unilaterally nephrectomised and, after an interval, one dog from each pair received a renal allograft from its fellow. The grafts were placed in the neck and no immunosuppression was used. The LMT was performed daily on recipient animals both before and after transplantation. Autologous donor-specific and homologous leucocytes, kidney, liver and skeletal muscle were used as sources of DL-A and organ-specific antigens. Inhibition of migration with donor-specific leucocyte and kidney antigens was observed prior to clinical evidence of rejection, which was confirmed histologically. Concurrently, inhibition was also observed with autologous kidney antigen and histological damage was noted in the recipient's own nontransplanted kidney accompanied by increasing proteinuria. Autologous serum withdrawn daily and added to the test culture medium abolished the inhibition of migration, suggesting the development of blocking factor. Preliminary studies in four patients after cadaveric renal transplantation demonstrate that a factor which abolishes inhibition of the LMT is present during clinical rejection episodes.

Turnover and distribution of platelets in patients with lupus nephritis. W. F. Clark, M. L. Lewis, J. S. Cameron and V. Parsons. Department of Medicine, Guy's and King's College Hospital and Department of Haematology, King's College Hospital, London, England. The survival of autologous platelets labelled in vitro with 32P was determined by serial blood samples with separation and counting of the washed platelets. When the disappearance curve was linear, survival time was determined by simple extension to zero activity; when it was curvilinear, the initial slope was extrapolated to zero. Serial external counting for 35Cr radioactivity was performed over the right kidney and spleen for five days. Six control subjects and 14 patients with systemic lupus and renal involvement were studied. In the control subjects platelet survival was 9.4 ± 0.5 (SEM) days. In eight patients with lupus and diffuse proliferative glomerulonephritis, the mean survival was 6.4 ± 1.1 days, and in one patient with lupus membranous nephritis, 7.5 days. In four patients with minor focal or no glomerular abnormalities, survival was 8.4 ± 0.4 days; and in a single patient who had been treated with dipyridamole and aspirin, with acute active lupus and diffuse proliferative nephritis, survival was 9.4 days. To assess renal uptake of platelets, the ratio right kidney/spleen at 50% survival over right kidney/spleen at 0 to 24 hr was calculated. This ratio averaged 0.50 ± 0.17 in the control subjects and was only 0.04 in a patient with idiopathic thrombocytopenic purpura. In the patients with lupus and diffuse proliferative glomerulonephritis, the ratio was 1.04 ± 0.25; in the patient with membranous nephritis, 2.50; and in three patients with minimal focal lesions, 0.85 ± 0.25. The results confirm that in patients with lupus nephritis, platelet survival is thought not to be a consequence of circulating anti-platelet antibody. The evidence suggests that platelets may be involved in soluble complex deposition in the kidney in human systemic lupus erythematosus nephritis. Alternatively, the kidney uptake of platelets could represent prominent platelet involvement in localized intrarenal coagulation or both.

Adaptations in metabolic acidosis: A reinterpretation. Edmund Bourke and Jane Oliver. Department of Medicine, Trinity College, Dublin, Ireland. The concept that increased ammonia secretion in acidosis results in increased H+ excretion derives from the practice of writing the formula of glutamine in the unionized from. At physiological pH glutamine is ionized, gives rise to NH3 (not NH3) and does not result in elimination of H+. An alternative interpretation is needed. Following oral administration of HCl to rats on a constant nitrogen intake, the enhanced ammonium excretion is coupled with an equimolar decrease in urea production falling by 32%, of control values. NH3/HCO3 administration did not alter urinary ammonium but was recovered as urea. By contrast, following NH4Cl administration, only 15% of the increased nitrogen load was recovered as urea, the remainder being accounted for as urinary ammonium. Arguments will be presented to support the following interpretation: Amino nitrogen is ordinarily converted to urea. Each turn of the urea cycle utilizes two bicarbonate ions. The subsequent metabolism of the remaining carbon skeleton generates bicarbonate. In HCl acidosis waste nitrogen bypasses urea synthesis to be excreted as NH3. No bicarbonate is utilized, but the carbon skeleton still generates bicarbonate. The HCO3 produced from conversion of NH3HCO3 to urea is balanced. Urea formation from NH4Cl utilizes net HCO3. The consequent acidosis causes a shift in disposal of waste nitrogen of amino acids from urea to urinary NH3 with generation of new CO2. Thus, total urea excretion is much less following NH4Cl than NH3HCO3. Inhibition of glutamine synthetase with methionine sulfoxamine decreased ammonium excretion in acidosis but did not effect the reduced urea production. This suggests a primary role for the urea cycle in adaptations to metabolic acidosis.

1-Alpha-hydroxycholecalciferol: A treatment for azotemic osteodystrophy. G. R. D. Catto, M. MacLeod, B. Pelle and E. Kodicek. Department of Medicine, University of Aberdeen
Scotland. It has been known for more than a century that patients with renal failure develop metabolic bone disease. The importance of this association has been appreciated only since recent advances in treatment have extended life expectancy and demonstrated that bone disease is an important factor in limiting the full rehabilitation of many patients. Investigation and management of the problem have been hindered until recently by the absence of a sensitive method for detecting in vivo small changes in the mineral content of bone. The most careful radiological assessment may not detect skeletal demineralization until as much as 30% of skeletal calcium has been lost. During the last 18 months, 19 patients receiving maintenance hemodialysis have been assessed for evidence of metabolic bone disease clinically, radiologically, histologically and by photon absorption and neutron activation techniques. Osteomalacia was the predominant abnormality noted on the bone biopsy samples. The rate of progression of the demineralizing condition has been accurately quantitated. Three patients with established, progressive metabolic bone disease have been treated with 1-alpha hydroxycholecalciferol, a synthetic analogue of the vitamin D derivative 1,25-dihydroxycholecalciferol, in an oral dose of 2 µg/day. In all three patients, absorption of calcium from the gastrointestinal tract and skeletal calcium content as measured by neutron activation analysis were increased.

Factors influencing the growth of children with chronic renal insufficiency. P. R. Betts, P. Howse and B. T. Rudd (Introduced by R. H. R. White). Children's Hospital, Birmingham, England. Growth retardation is a frequent finding in children with chronic renal insufficiency. Studies of the growth patterns of 33 such children have shown that the development of impaired renal function in infancy has a more deleterious effect upon linear growth than its onset in later years. A reduction in the growth velocity of these children occurred once the glomerular filtration rate fell below 25 ml/min/1.73 m² or their energy intake was below 80% of that recommended for age (Betts & Magrath, 1974). It has been demonstrated that “catch-up” growth does not necessarily occur following renal transplantation. Studies have shown that the growth potential of the 33 children, as expressed by their height for bone age, diminished as chronological age increased. This may have implications for the optimal age for transplantation in children. It has previously been suggested that elevated circulating corticosteroids, which have been found in uremic adults, may be partially responsible for growth retardation in children. However, these results were determined using a fluorimetric technique. We have studied the serum cortisol concentrations by the more selective technique of competitive protein binding and found no evidence of elevated serum cortisol concentrations in these children.