**1636** AUTONOMIC DYSFUNCTION - A MECHANISM FOR RENAL FAILURE? Robert G. Schacht, Felicia Axelrod and David S. Baldwin, New York University Medical Center, Departments of Pediatrics and Medicine, New York.

Familial dysautonomia, a rare autosomal recessive disorder, is characterized by a complex clinical symptomatology related to widespread autonomic and sensory dysfunction. We have previously reported renal failure due to intra-renal vascular and glomerular sclerosis in one dysautonomic; in all, 9 patients whom we have followed up to 18 years of age or more have become uremic. In the present study, renal hemodynamcis were found to be consistently reduced in a group of dysautonomics who were studied at random.

Among the 13 patients, aged 7 to 38 years, all had either persistent or episodic hypertension typical of dysautonomia. Glomerular filtration rates ($C_{IN}$) ranged from 107 down to 20 ml/min/1.73m$^2$ ($\bar{x}$ = 70). Renal plasma flows ($C_{PAH}$) were reduced to levels ranging from 560 to 72 ml/min/1.73m$^2$ ($\bar{x}$ = 350). Filtration fractions averaged 21%. Reductions in GFR and RPF increased with age. Decreased levels of PRA and aldosterone were found in 8 of 12 patients.

We have documented depressed renal hemodynamics and progression to uremia in familial dysautonomia. Intermittent hypertension and failure of autoregulation resulting from renal denervation could expose the kidney to vascular and glomerular damage due to hydraulic stress. Dysautonomia may represent a model in man which depicts the key of hemodynamic factors in the causation of glomerular injury.

**1639** $CO_2$ CAUSES EXOCYTOSIS OF VESICLES CONTAINING $H^+$ PUMPS IN ISOLATED SEGMENTS OF COLLECTING DUCT (CD) AND PROXIMAL STRAIGHT TUBULE (PST). George J. Schwartz and Qais Al-Awqati, Albert Einstein College of Medicine, Dept. of Pediatrics, Bronx, N.Y. and Columbia University, Dept. of Medicine, N.Y., N.Y.

$CO_2$ directly stimulates $H^+$ secretion, possibly by causing an increase in the number of $H^+$ pumps in the luminal membrane. In order to test this hypothesis we perfused CD and PST on the stage of an inverted epifluorescence microscope with fluorescein isothiocyanate dextran (mw 70,000) in $CO_2$-free medium. Uptake of this substance can only occur by endocytosis. After wash out we noted punctate fluorescence in endocytic vesicles in some CD and in all PST cells. More cells took up fluorescent dextran in medullary than in cortical CD, consistent with the greater rate of $H^+$ secretion in medullary CD. Using the pH dependence of the excitation spectrum of the fluorescence we found the pH of the vesicles to be acid (c. pH 6). Addition of $NH_3$ or nigericin increased vesicular pH by 0.6 ± 0.2 units, suggesting that the acidity of the vesicles was due to $H^+$ pumps. $CO_2$ added isohydrically to the medium reduced fluorescence intensity by 25±7% in CD and 29 ± 5% in PST. Since this effect was prevented by colchicine added to the bath, we believe that $CO_2$ causes a decrease in cytoplasmic fluorescence by stimulating exocytic fusion of the vesicles. We conclude that some cells in CD and all cells in PST incorporate fluorescent dextran into the apical cytoplasmic vesicles and acidify them with $H^+$ pumps. $CO_2$ causes fusion of these vesicles with the luminal membrane and thus stimulates $H^+$ secretion, at least in part, by increasing the number of functioning $H^+$ pumps.

**●1637** SOLUBLE IMMUNE RESPONSE SUPPRESSOR (SIRS) IN URINES OF NEPHROTIC PATIENTS. H.William Schnaper and Thomas M. Aune. (Spon. by Barbara R. Cole.) Washington Univ. Sch. of Med. and Jewish Hosp. of St. Louis, St.Louis, MO

Patients with nephrotic syndrome (NS) have decreased experimental immune responsiveness; the cause of this is unclear. Urines from children with steroid-responsive NS (SRNS) were evaluated for activity of SIRS, a lymphokine which nonspecifically suppresses in vitro antibody-producing responses when added early in the culture period. After activation by $H_2O_2$ ($10^{-6}$M), $SIRS_{ox}$ suppresses when added shortly before assay. SIRS is inhibited by catalase, 2-mercaptoethanol (2-ME) or levamisole.

Dialyzed, lyophilized urine (10-100 µg/culture) resuspended in culture medium was added to 7-day pokeweed mitogen-stimulated lymphocyte cultures, and polyclonal IgM plaque-forming cell (PFC) responses were determined. Urine from 6 of 7 patients with SRNS, but not from healthy controls or patients with focal glomerulosclerosis or acute nephritis, suppressed PFC responses by 60-80%. Like human SIRS, the suppressor substance had a mol. wt. of 110-150 kd and was inactivated by pH2 and protease. It suppressed only when added near culture initiation; however, factor activated with $10^{-6}$M $H_2O_2$ suppressed responses when added within 24 hrs. of assay. Suppression was blocked by catalase, 2-ME and levamisole. This increased urine SIRS activity may be related to the immunosuppression observed in SRNS patients. In a patient studied serially, suppressive activity disappeared from the urine after initiation of treatment but before remission of NS. (Supported by Council for Tobacco Research, USA, Inc. Grant No. 1431.)

**1640** MATURATION OF THE CHEMICAL FORCE DRIVING $K^+$ SECRETION IN THE CORTICAL COLLECTING TUBULE (CCT). Lisa M. Satlin and George J. Schwartz, Albert Einstein College of Medicine, Department of Pediatrics, Bronx, N.Y.

The serum $K^+$ concentration in the newborn is higher than in the adult, possibly resulting from a diminished $K^+$ secretory rate in the immature nephron. Since $K^+$ secretion is driven, in part, by the cell-to-lumen concentration gradient, a diminished intracellular $K^+$ concentration (Ki) may limit $K^+$ secretion in the newborn. We therefore measured Ki in rabbit CCTs at three developmental stages. We dissected CCTs in an isotonic choline chloride solution, measured length and outer diameter, and placed them in 0.1M trichloroacetic acid for 24 hours. $K^+$ and $Na^+$ concentrations of the tubular extract were measured with a helium glow photometer. In order to calculate Ki, the volume of water in 1 mm of CCT was assumed to be 80% of tubular volume.

| Age | n | Cell Water (nl/mm) | $K^+$ (pmol/mm) | Ki (mEq/L) |
|---|---|---|---|---|
| Newborn | 9 | 0.34 ± .02 | 38.7 ± 2.9 | 112 ± 10 |
| 1 Month | 14 | 0.56 ± .05 | 44.1 ± 2.6 | 79 ± 5 |
| Adult | 13 | 1.01 ± .04 | 81.3 ± 8.8 | 81 ± 9 |
| p value | | < 0.001 | < 0.001 | < 0.02 |

Ki in the CCT is, if anything, higher in the newborn than in the adult. In addition, the cellular $Na^+/K^+$ ratio does not change during development (newborn=0.11 ± .04 vs. adult=0.16 ± .05, p=0.3). Assuming that $K^+$ activity bears a constant relationship to Ki during development, we suggest that changes in the tubular flow rate, transepithelial voltage, and/or membrane $K^+$ permeability, rather than in Ki, mediate the maturation of $K^+$ secretion by the CCT.

**●1638** WATER AND SOLUTE FLUXES ACROSS ISOLATED RABBIT ILEUM: MODEL OF ILEAL BLADDER. Morris J. Schoeneman, Irvin Hirsch, Elliot Leiter, (spon. by Walter L. Henley); Mount Sinai School of Medicine; Beth Israel Medical Center; Depts. of Pediatrics and Urology. New York, N.Y. 10003.

Metabolic complications such as salt and water overload often follow uretero-sigmoid diversion in children. These problems occur less with uretero-ileal conduits, but external appliances and loss of continence affect quality of life. A continent ileal bladder has theoretical advantages, but has not been studied. We designed an animal model of salt and water transport in 2 types of ileal urinary diversion. Ten cm loops of ileum were exteriorized in rabbits. A hypertonic urine-like solution (NaCl 10gm/L; urea 30gm/L; $KH_2PO_4$ 1.6gm/L; 840mOsm/L) labeled with phenol red was infused into the loops under conditions of 1) constant perfusion at 0.5ml/min (ileal conduit model) and 2) 2 & 4 hour dwell periods of 17ml within the loops (ileal bladder model). Net fluxes of sodium, chloride, potassium, and water were calculated for both models, as were changes in osmolarity and urea content. Net secretion of water (0.011±0.002(ml) ($cm^{-1}$) ($min^{-1}$) and Na+ (0.32± 0.2(uEq)($cm^{-1}$)($min^{-1}$) into the loop occurred in both models, with variable small fluxes of $K^+$ and chloride. Sodium secretion was significantly greater in the bladder model than in the conduit. No significant difference in flux between 2 & 4 hour dwell periods was noted. We conclude that there is no net salt and water absorption in this model of an ileal bladder, and the frequency of emptying the bladder need be no more than every 4 hours. A continent ileal bladder may therefore be feasible in children requiring diversion.

**1641** THE EFFECTS OF $1,25(OH)_2D_3$ ON TISSUE AND BONE METABOLISM IN THE UREMIC RAT MODEL. AB Sedman,* NL Miller* B Buddington,* GM Lum, AC Alfrey,* Dept Medicine and Pediatrics, University Colorado School Medicine, Denver, Colorado.

Therapy with $1,25(OH)_2D_3$ to prevent osteodystrophy in renal failure patients can cause hypercalcemia, soft tissue calcification, and decreased creatinine clearance. To test whether low dose therapy with $1,25(OH)_2D_3$ could prevent decreased mineralization in uremia without concomitant hypercalcemia, we studied 2 groups (A & B) of 13 rats with remnant kidney and 8 non-remnant controls (C). Groups A & B received 0 µg and .01 µg/Kg/day of $1,25(OH)_2D_3$ respectively. Results: Weekly serum calcium (Ca), phosphorus, creatinine, body weight (wt) were not significantly different between Groups A & B. Analysis after sacrifice at 16 weeks (mean ± 1 SD) showed:

| | A | B | C |
|---|---|---|---|
| Femur Wt (g) | .73±.12† | .82±.06 | .84±.06 |
| % Ash (mg ash/mg bone) | 70.1±.95† | 71.5±1.08 | 71.3±.66 |
| Heart Ca (mEq/Kg) | 78±230 | 26±27 | 9.4±0.6 |
| Kidney Ca (mEq/Kg) | 219±478 | 231±313 | 19±2† |
| Aorta Ca (mEq/Kg) | 189±359 | 580±911 | 28±4† |
| Lung Ca (mEq/Kg) | 152±409 | 75±92 | 32±3 |
| Creatinine (mg/dl) | 1.87±.91 | 1.85±.79 | .56±.12† |

† Significantly different from other groups ($p < 0.05$)
Creatinine correlated inversely with % ash (r=0.77), and femur wt correlated with body wt (r=0.95) in A but not in B. Conclusion: $1,25(OH)_2D_3$ prevented decreased bone mineralization associated with uremia without a significant increase of hypercalcemia, soft tissue calcification, or serum creatinine.