1573 REGRESSION OF CONGENITAL MURINE POLYCYSTIC KIDNEY DISEASE (PKD) IN METANEPHRIC ORGAN CULTURE (MOC).

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A form of autosomal recessive PKD naturally occurs in the mutant CPK strain of C57BL/6J mice. In order to examine the role of enviromental factors in the expression of genetically determined PKD, the organogenesis of CPK kidneys was studied in our previously described MOC system (In Vitro 18:675, 1982). In this system, advanced murine nephrogenesis occurs in a serum-free, completely controlled biochemical environment.

Newborn kidneys from controls (CON) and CPK mice were microsliced into 100 μm explants and cultured in Ham's F-12: DMEM supplemented with insulin (8×10^{-7} M), T_3 (2×10^{-9}M),transferrin (6×10^{-8} M), PGE_1 (7×10^{-8} M), and Na_2SeO_3 (7×10^{-9} M) at 36 ± 0.5°C in mixed air:5% CO_2. During 120 hours of culture:1) CON explants increased in size and demonstrated advanced tubular differentiation; and 2) CPK explants, which initially exhibited prominent proximal tubular dilatation and cyst formation, demonstrated total cyst regression in addition to overall growth and differentiation similar to CON.

We conclude that in the CPK animal model of PKD: 1) early changes of proximal tubular cyst formation are totally reversible in vitro; and therefore that 2) genetically determined cyst formation can be modified by environmental factors. MOC of CPK kidneys provides a controlled experimental system in which the enviromental factors modulating cystic organogenesis may be isolated and further characterized.

1574 MULTICENTER STUDY OF SERUM ERYTHROPOIETIN AND PTH LEVELS IN CHILDREN WITH CHRONIC RENAL FAILURE.

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The relative roles of erythropoietin (Ep) deficiency and PTH excess in the development of anemia in children with chronic renal failure (CRF) have been assessed. Serum Ep in 71 patients (PTS) was determined by radioimmunoassay (RIA). Seven were studied in the predialysis stage, 32 on hemodialysis, 16 on CAPD and 16 on CCPD. The mean serum Ep was 38.1+3.5 mu/ml with anemia of renal disease (predialysis and dialysis PTS) compared to 19.6 ±1.5 mu/ml in normals. However, when compared to 30 children with anemia of non-renal origin, the elevation in Ep (range 28.7-327 mu/ml) was significantly below that expected for the degree of anemia in these renal disease PTS. We also found a direct inhibitory effect of uremic serum on both immunologic and biologic activity of Ep itself. Co-incubation of Ep (50,100, or 200 mu/ml) with uremic serum resulted in markedly lower RIA values for these three concentrations of Ep compared to normal serum. Biologic activity as assessed in the fetal mouse liver CFU-E assay was also decreased with uremic serum. Serum PTH levels, although elevated, did not correlate with the degree of anemia. In conclusion although relative Ep deficiency plays a primary role in the anemia of CRF other factors which alter Ep itself and inhibit erythroid progenitors appear to be involved.

†1575 IDIOPATHIC NEPHROTIC SYNDROME: LONG-TERM PROGNOSIS.

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The clinical course of idiopathic nephrotic syndrome (NS) was studied in 65 children (mean age 3.3 yrs, range 1-14 yrs) who were either steroid responsive (61 pts) or had steroid-resistant minimal change disease (4 pts) at onset. All pts were followed for a minimum of 10 yrs (range 10-25 yrs) and follow-up was 15 yrs in 29 pts (45%).

Of the 61 steroid responsive pts, 53 had a frequently relapsing-steroid dependent course. Of these pts, 20 were treated with cytoxan which induced a permanent remission in 13 (mean duration 8.7 yrs, range 6-12 yrs) and significantly reduced the rate of relapses in 4 others. Of the 33 pts not given cytoxan, 35% continue to experience relapses 10-18 yrs after onset while the others have been in remission for the past 2-16 yrs (mean 7.6 yrs).

Of the 4 pts with steroid resistant minimal change disease, 3 were treated with cytoxan and all achieved a remission. Two of these pts have had no relapses 10 and 12 yrs after onset and 1 pt had a single relapse.

At the completion of follow-up (mean 14.4 yrs), all pts have normal renal function (S_{cr} < 1.5 mg/dl), 17% have BP ≥ 140/80 and 76% have a height which is < 50%tile (adjusted for sex and age) while 33% are < 25%tile for height. These findings suggest that in children with steroid responsive NS or steroid resistant minimal change disease there is: a) a favorable long-term outcome; b) the duration of relapsing disease is reduced by treatment with cytoxan and c) short stature is a significant consequence of therapy.

●1576 PHYSIOLOGICAL FACTORS IN POSTNATAL DIURESIS IN PRETERM INFANTS.

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Abrupt increase in urine output in preterm infants on 2nd-3rd day of life has been documented. To determine the etiology of this diuresis, sequential changes in renal function during the first five days were studied in 21 preterm AGA infants with gestational age 30.2±.4wks. Infants were entered into the study within 24hrs of life and urine collections were divided into 10 consecutive 12hr periods for 5 days. Diuresis was defined as urine volume (V) ≥ 3ml/kg/hr and output/intake ratio ≥ 1. 16 infants had distinct diuresis, as defined by above criteria. Median diuretic period occurred between 36 and 48 hrs. (Mean 45 hrs)

	Prediuretic	Diuretic	Post diuretic
Age (hrs)	12-24	36-48	108-120
V (ml/hr/kg)	2.0 ± 0.3	6.4 ± 0.6*	5.0 ± 0.4*
GFR (ml/min/1.7M^2)	8.5 ± 0.13	16.1 ± 2.2*	12.6 ± 0.9
FENa (%)	1.2 ± 0.2	3.4 ± 0.6*	3.1 ± 0.3
FEK (%)	30.3 ± 4.5	32.3 ± 4.4	25.8 ± 2.6
Uosm (mosm/kg H_2O)	189 ± 19	149 ± 10	160 ± 10

* P<.01 compared to previous period. (ANOVA w/repeated measures.)

These results indicate that the low urine output in prediuretic period is not due to high ADH effect (note low Uosm throughout). Diuresis is due to an abrupt rise in GFR which is not simply maturational but more likely hemodynamic, since GFR is actually lower in post diuretic period. Finally, diuresis is due also to decreased tubular reabsorption, most likely in proximal tubule or Henle's loop, since both Na and K excretion were high during diuresis.

† 1577 **ALDOSTERONE METABOLISM AND Na TRANSPORT.**

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Recent studies have demonstrated that aldosterone (aldo) is transformed into a number of metabolites by nuclei and plasma membranes of mammalian kidney cells (J. Steroid Biochem. 19:1205, 1983). In mammalian kidney, aldo not only promotes Na^+ reabsorption but also secretion of K^+ and H^+, most probably reflecting functions of several cell types. In order to study the effects of transformation on Na^+ transport alone, aldo metabolism was examined in a more elemental Na^+ transporting aldo responsive epithelia, the toad urinary bladder (Bufo marinus). After depletion of endogenous aldo, bladders were incubated with ^{3}H aldo for either 1 or 5 hrs. Tissues were analyzed for aldo metabolites using high resolution HPLC. In separate experiments, Na^+ transport was assessed by the short circuit current (SCC) technique. After 1 hr of ^{3}H aldo exposure (a latent period prior to an aldo induced rise in SCC), tissues transformed about 10% of the labelled hormone into a polar mono-sulfated aldo and a variety of 5-α reduced aldo products including 5α dihydroaldo (DHA); 3α,5α tetrahydroaldo (THA); and 3β, 5α THA. 5α DHA possess significant antinatriuretic activity in kidney and toad bladder. Following a 5 hr tissue incubation (a time of peak aldo rise in SCC), about 25% of the ^{3}H aldo was converted into the same compounds as in the 1 hr study. The spironolactone, K-canrenoate (3.5×10^{-4}M) inhibited aldo (10^{-7}M) stimulated SCC by 56±6% (p<0.001; n=6) and eliminated ^{3}H aldo metabolism at both 1 & 5 hrs. K-canrenoate had no effect on either basal or vasopressin stimulated rise in SCC. We conclude that aldo metabolic transformation begins prior to aldo induced increases in Na^+ transport. Both the generation of aldo metabolites and the increase in Na^+ transport can be selectively inhibited by K-canrenoate. We speculate that one or more of these aldo metabolites may mediate or regulate aldo action in this tissue.

† 1578 RAPID GROWTH IN YOUNG CHILDREN AFTER RENAL TRANSPLANTATION USING CYCLOSPORINE (CsA) AND PREDNISONE (PRED).

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Pediatric patients, 2-20 y.o., who received renal transplants (TX) after Jan,1984, were treated with CsA+PRED immunosuppression. Oral CsA was initiated at 14mg/kg/d and tapered individually by clinical course and trough serum CsA (SCsA), to 7-9mg/kg/d by 6 mon. High dose PRED, 2-3mg/kg/d, was begun the day of surgery, tapered to 1mg/kg/d by 1 mon and maintained at low dose, 0.2-0.4 mg/kg/d, after 2 mon. Nine grafts are all functioning after short term follow-up (F/U) (54 patient mon). The youngest recipients, ages 2-6 y.o. (n=5:4 LRD,1 CAD), demonstrated rapid growth rates, 0.96-1.25cm/mon, during 4-9 mon F/U. Estimated GFR at last F/U was 75-109ml/min/1.73m^2 (range Scr 0.5-0.8mg/dl). One patient experienced reversible acute rejection at 2 mon, but still grew rapidly (1.25cm/mon). No young child had CsA nephrotoxicity. Trough SCsA was always <85ng/ml. Older children grew less well. An 11 y.o. LRD recipient with Scr 1.8mg/dl and GFR 43ml/min/1.73m^2 grew 0.5cm/mon during 8 mon F/U. Three older recipients (15-20 y.o.:1 LRD,2 CAD) had bone age >13 y.o. and demonstrated little growth (0-0.16cm/mon) in 3-8 mon F/U; Scr was 1.4-2.2mg/dl and GFR 55-58ml/min/1.73m^2. One had reversible acute rejection during wk one. Another had reversible CsA nephrotoxicity. Other CsA toxic side effects were hirsuitism (9/9), hand tremor (5/9) and asymptomatic high serum uric acid (6.7-13.5mg/dl) (9/9). Our experience suggests CsA+PRED in pediatric TX recipients 1) permits rapid growth, especially in young children, 2) is not limited, at least initially, by nephrotoxicity and 3) leads to early successful pediatric TX outcome.