NEPHROLOGY

The natural history of renal tubular acidosis: Lightwood's syndrome revisited. MARTIN A. NASH, ANTONIO D. TORRADO, EDDIE S. MOORE, JUAN RODRIGUEZ-SORIANO, IRA GREIFER, ADRIAN SPITZER, and CHESTER M. EDELMANN, JR. *Albert Einstein Coll. of Med., N. Y., N. Y.*

Twelve children with primary renal tubular acidosis (RTA) studied with HCO_3^- titration and NH_4Cl loading have been observed 1½–8 yrs. These include 7 ♂ with proximal RTA (PRTA) dx'd at 7–18 mos, and 3 ♂ and 2 ♀ with distal RTA dx'd at 3–13 yrs. Bone disease and/or nephrocalcinosis were present in DRTA but not PRTA. GFR (C_{IN}) at onset was normal or slightly decreased in PRTA, but 40–60% of normal in DRTA. GFR is now normal in all patients. With rx pts had accelerated growth, reaching at least the 3rd percentile in 2–3 yrs, with some achieving the 50th percentile. Five with PRTA have normal blood pH and HCO_3 off rx, 5–8 yrs after dx. Two remain on rx <2 yrs after dx. The acidification defect in pts with DRTA persists. Thus PRTA appears to be a self-limited disease of bicarbonate reabsorption in male infants, characterized by growth retardation and acidemia, without bone disease and nephrocalcinosis. DRTA appears to be a permanent defect in urinary acidification, with acidemia, growth retardation, bone disease, and nephrocalcinosis. Response to rx in both groups is good, with marked improvement in growth, and normalization of GFR in DRTA despite severe degrees of initial nephrocalcinosis. On the basis of these observations, it seems likely that Lightwoods's syndrome was proximal RTA—not distal RTA as has been considered heretofore.

Maturation of intrarenal blood flow distribution in newborn puppies. LEONARD I. KLEINMAN and JOHN H. REUTER (Intr. by I. Light). *Univ. of Cincinnati Coll. of Med., Cincinnati, Ohio.*

Intrarenal glomerular blood flow distribution was studied in 34 newborn puppies ranging in age from 1 to 40 days using radiolabeled carbonated microspheres 15–25 μ. The technique was validated by histological sectioning, dual labeling of microspheres and multiple sectioning of the same kidney. Relative blood flow per gram tissue to juxtamedullary inner cortical (IC) and outer cortical (OC) glomeruli was determined by the ratio of microspheres trapped in the respective region. IC/OC ratios fell from 1.2 at birth to 0.25 at 14 days and remained relatively constant thereafter. There was no correlation between IC/OC ratio and PAH extraction (EPAH). EPAH remained constant at 0.50 during the first 40 days of life (adult EPAH = 0.85). IC/OC ratio declined as blood pressure rose from 30 to 70 mm Hg and remained relatively constant at blood pressures above 70 mm Hg. These results suggest that there is a marked change in intrarenal blood flow distribution during the first two weeks of life as more blood is delivered to outer cortical nephrons with maturation. The early large flow to juxtamedullary glomeruli suggests a large postglomerular medullary flow. The lack of correlation between IC/OC ratio and EPAH suggests that the low EPAH in the newborn period is not due solely to a large medullary flow. Finally, intrarenal flow distribution maturation is closely related to blood pressure maturation.

The effect of Na_2SO_4 on urinary acidification in the intact fetal lamb. EDDIE S. MOORE, CLARENCE W. DELANNOY, and JOHN B. PATON (Intr. by Richard Behrman). *Univ. of Ill. Coll. of Med. Chicago, Ill.*

Recent studies have shown that the fetal kidney is limited in its ability to acidify the urine and to secrete hydrogen ions when compared to the adult kidney. To further study H^+ secretion and the ability of the fetal kidney to establish a pH gradient between blood and urine, Na_2SO_4 was infused into the intact fetus.

Studies were done on 7 near-term pregnant sheep and their fetal lambs. The ewes were injected with DOCA and the fetuses were given cortisone acetate. This served to enhance renal tubular reabsorption of Na^+. Caesarean sections were performed and 75cc of 8% Na_2SO_4 was infused into each *fetus*. Blood and urine samples were collected from the ewe and fetus. There were no significant changes in fetal or maternal blood pressure, pulse, temperature or pCO_2.

The mean initial urine and blood pH in the fetus was 7.075 and 7.352 respectively. The mean *minimum urine pH* in the fetus after Na_2SO_4 was 5.2 with a range of 4.7–5.7. The mean minimum blood pH in the fetus after Na_2SO_4 was 7.362. The mean urine pH in the ewe before and after Na_2SO_4 was 5.824 and 5.920 respectively. This is consistent with little or no transfer of $SO_4 =$ across the placenta. The mean maximum TA and NH_4 excretion in the fetus was 4.35 and 8.21 μEq/min/kg respectively. There was no correlation between fetal weight and response time before production of an acid urine.

These studies indicate that in the intact fetal lamb, a stimulus (DOCA) to the fetal kidney to reabsorb Na^+ without equivalent amount of anion results in intense acidification of the urine. The fetal kidney is thus able to establish a pH gradient with no evidence of intrinsic limitation of hydrogen ion secretion.

Pressure gradients for filtration in the developing kidney. ADRIAN SPITZER (Intr. by Chester M. Edelmann, Jr.). *Albert Einstein Coll. of Med., N. Y., N. Y.*

It is well documented, both in humans and animals, that low rates of glomerular filtration prevail during early postnatal life. Although several explanations for this phenomenon have been offered, no direct measurements of the forces responsible for glomerular filtration in the developing animal are available. This information was sought in the present study by micropuncture techniques. Free flow proximal intratubular pressure (P_f), "stop flow" (P_s), mean arterial, and colloid-osmotic pressure of the plasma protein (P_{co}), were determined in guinea pigs ranging in age from 1 to 56 days (27 animals). The values obtained were used in the calculation of glomerular capillary pressure, $P_{cap} = P_s + P_{co}$, and of the effective filtration pressure, $P_{eff} = P_{cap} - (P_f + P_{co})$. Free flow intratubular pressure increased from 5.5 ± 0.3 during the 1st to 9.2 ± 0.2 (mean ± S. E.) during the 8th week of life, whereas capillary pressure increased from 21.2 ± 1.8 to 29.3 ± 1.0 mm Hg. Since the actual increase in capillary pressure was about twice the increase in intratubular pressure, effective filtration pressure rose accordingly from 4.9 ± 0.4 to 9.4 ± 0.8 mm Hg. During the same period mean arterial pressure changed from 42.9 ± 2.2 to 58.5 ± 7.9 mm Hg. It appears, therefore, that an increase in glomerular capillary pressure is an important factor in the increase in glomerular filtration rate that is observed with age.

Ontogeny of amino acid transport sites in kidney: specific and total activity. K. BAERLOCHER, C. CLOW, S. MACKENZIE and C. SCRIVER. *McGill Univ.-Montreal Children's Hosp. Res. Inst., Montreal, Que., Can.*

Urinary hyperexcretion of proline, hydroxyproline and glycine is a defined component of the transient impairment in tubular

absorption of amino acids after birth in man and rat. In both species, loss of iminoaciduria precedes reduction of hyperglycinuria. This coincides with in vitro evidence in rat for phased "activation" of substrate-specific membrane carriers, the one for proline appearing early, that for glycine, late. "Activation" apparently involves appearance of new carrier proteins rather than gain in energy coupling to existing carriers, since studies of amino acid interaction during influx, heteroexchange and inhibition of energy metabolism indicate a specific initial lack of relevant carriers. However "maturation" of total amino acid transport in kidney also involves another component. By comparing Vmax for uptake in vitro of proline, glycine and α-amino isobutyric acid on carriers present from birth, we found their relative capacities to increase synchronously after birth. This is compatible either with increasing membrane area or with more efficient coupling of energy to transport. Thus changes both in specific activity of carriers and in total membrane activity characterize ontogeny of amino acid transport in kidney.

Clinical-pathological correlations in the nephrotic syndrome. A report of the international study of kidney disease in children. CHESTER M. EDELMANN, JR., *A. Einstein Coll. Med., N. Y.*

191 children with idiopathic nephrotic syndrome (absence of systemic disease or other known etiology) were studied from onset. Age and sex distribution were as expected. Renal biopsy revealed glomerulonephritis (GN) in 1/5; of these 4/5 were steroid nonresponsive (continued proteinuria after 8 weeks prednisone). Of patients with "minimal lesions" (ML), 5% were steroid nonresponsive; the other 95% were 1/3 frequent relapsers, 1/3 infrequent relapsers, and 1/3 nonrelapsers. In ML no difference in response or course was found with sex or age of onset. The overall poorer prognosis in ♀ and in older children was due to underlying GN. Only 38% with ML, but 52% with GN were ♀. >1/2 patients >8 years old had GN. Hematuria did not predict the clinical course in ML. Marked hematuria was present in 19% with ML but 64% with GN. Thus the poor prognosis associated with hematuria is due to the likelihood of underlying GN. Despite striking exceptions, urinary selectivity index correlated in a general way with pathology and steroid response. Immunization preceded onset only in patients with ML, suggesting that it may be an etiologic factor. No correlations with histology or course were found with history of allergy in patient or family, infection preceding onset, urinary tract infection at onset, or family history of renal disease. Although histology between groups based on father's occupation was similar, there were significantly more nonrelapsing patients in the professional group.

Correlations of selectivity of protein excretion in childhood nephrotic syndrome. JOHN T. HERRIN, and A. SALTZMAN (Intro. by John D. Crawford). *Harvard Med. Sch., Mass. Gen. Hosp., Children's Service, and Shriner's Burns Institute, Boston, Mass.*

Selectivity of proteinuria as measured by clearance ratios of transferrin and IgG were performed in 28 children with nephrotic syndrome. Selectivity correlated with response to steroid therapy, histology when available (16 patients) and was not related to degree of proteinuria or altered by therapy.

Radial diffusion methods (Mancini) using commercially prepared plates and values using the Ouchterlony method gave comparable results which remained constant, within the limits of the method throughout repeated testing.

Critical evaluation of results shows that high protein excretion is necessary for accurate prediction of steroid response. Preliminary studies suggest that calculation of selectivity is possible even at low levels of protein excretion by comparison of clearance of transferrin, IgG and α_2 macroglobulin performed on urine, in which the protein has been concentrated by lyophylization.

Plasma norepinephrine concentration before and after albumin infusion in nephrotic children. ROBERT C. KELSCH, GERALD S. LIGHT, and WILLIAM J. OLIVER. *Univ. of Mich. Med. Ctr., Ann Arbor, Mich.*

A reduction of effective plasma volume secondary to a decrease in the quantity of circulating protein is postulated to initiate edema formation in the nephrotic syndrome, however reduction of plasma volume has not been consistently demonstrated during active disease. Acute and chronic reduction of plasma volume is associated with an increased excretion of norepinephrine, presumably secondary to increased sympathetic activity. We therefore studied certain aspects of norepinephrine metabolism in thirteen children with the active nephrotic syndrome. All children were on a 1½–2 mEq/kg/day sodium intake and no diuretic therapy. Plasma norepinephrine concentration was measured on two consecutive mornings and again four hours later each day. Albumin (6–18 grams) was infused 3 hours prior to the second blood sample on the second day. All samples were obtained from the antecubital vein after the subject had remained at 30 degrees tilt for 20 minutes. Eight of the thirteen children had increased plasma norepinephrine concentrations in the early morning (> 0.5 ng./ml). The plasma norepinephrine concentration measured following albumin infusion was significantly reduced whereas that obtained on the control day was not. Urinary excretion of conjugated norepinephrine declined significantly within 48 hours after the initiation of prednisone treatment in these subjects. These data suggest the presence of increased sympathetic activity during the active phase of the nephrotic syndrome which can be altered by the infusion of albumin or the administration of prednisone.

Familial nephrotic syndrome with nephrocalcinosis and tubular dysfunction. EDMUND C. BURKE, GUNNAR B. STICKLER, KEITH E. HOLLEY, and LADISLAV P. NOVAK, *Mayo Clinic and Mayo Found., Rochester, Minn.*

We have studied 5 children in 2 families, 3 boys in family A and 2 girls in family B, who had the onset of nephrotic syndrome in early infancy. The syndrome proved to be steroid-resistant, although there was no evidence of tubular failure initially. Growth retardation, renal osteodystrophy, and tetany appeared in several at an early age, and all manifested these symptoms eventually. Glycosuria, aminoaciduria, and nephrocalcinosis also appeared. Renal biopsies from 2 children in each family showed glomerular proliferative changes, glomerular scarring, interstitial inflammation, and microcalcinosis together with marked tubular atrophy. Autopsy studies were completed on 2 boys. Each boy died when about 8 years old. One girl is preterminal with renal failure at 8 years of age. Hypertension was present only terminally. The youngest boy in family A has not yet developed nephrocalcinosis. Total-body composition studies on 1 boy and 2 girls showed increased exchangeable sodium, increase in extracellular water, decrease in total body potassium, and decrease in intracellular potassium. Whereas tubular failure previously has been reported in patients with long-standing nephrotic syndrome, we believe these cases differ in that they are familial and have interstitial nephritis and nephrocalcinosis.