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Abstracts

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A

PAEDIATRIC NEPHROLOGY ON THE THRESHOLD OF EUROPEAN INTEGRATION, Cyril Chantler, United Medical and Dental Schools of Guy's and St Thomas's Hospitals, Guy's Hospital, London SE1 9RT, United Kingdom

The intention is to encourage a debate about the problems that face Paediatric Nephrology in Europe during the next decade. Tentative suggestions will be made concerning ways in which problems identified might be solved.

The Role of the Paediatric Nephrologist
The Paediatric Nephrologist is the doctor who carries the ultimate responsibility for the medical care of a child with kidney disease. Obviously many children with kidney disorders will be cared for by doctors other than paediatric nephrologists, but the paediatric nephrologist as well as assuming direct responsibility for the care of children with serious kidney disease should also provide an advisory service for paediatric nephrology in the region where they work. It is important to determine the training and experience required; a thorough grounding in both paediatrics and nephrology is essential.

Clinical Efficiency and Clinical Effectiveness
There is no country in the world where there is sufficient money to meet all possible demands for health care for the whole population. Obviously the discrepancy between what could be done and what is available is very different in different economies but the approach to the problem is similar. The problem of finance is particularly relevant in paediatric nephrology where the cost of treatment to the child with chronic renal failure is huge. It is necessary for all doctors to review their practice to encourage maximum economic efficiency in the delivery of care and ensure that treatment is effective. The ESPN and the national societies can encourage research into clinical effectiveness by means of controlled trials and audit of outcome. This research should be linked to studies of cost effectiveness. Consideration should be given to setting up an audit unit under the auspices of the ESPN to encourage these activities.

Developing Economies
It is easy to be depressed by the lack of resources and the anxieties of colleagues from Eastern Europe should not be under-estimated. Many countries with low expenditures have more doctors and nurses than higher spenders, and more hospital beds. A significant proportion of the extra money spent on health care by richer countries goes on higher salaries for health workers. The most important change required is to translate the new freedoms into medical practice, individual initiatives must be encouraged with release from constraints of central control and tradition. Resources can be released by developing new patterns of care. Technology which is robust rather than sophisticated should be sought and the ESPN might help by encouraging twinning of units in Western and Eastern Europe.

Organisation of services
Principles regarding the provision of services for children with kidney disease should be developed. The role of the paediatric nephrologist as a member of a multi-disciplinary team should acknowledge the important contributions of other professionals, such as nursing, dietetics, social workers, etc. Close relationships with general paediatric services and adult nephrology services are desirable to improve the quality and cost effectiveness of the work. The technology required for a full paediatric nephrology service is expensive and it is difficult to justify small isolated childrens units. There is increasing evidence that small volume providers are economically inefficient and have less good outcomes per treatment than large volume providers. Services should concentrate on the needs of children and families and represent a reasonable balance between convenience and cost. Good practice can be promoted by financial and professional means and by auditing the outcome of treatment.

Action
The role of the ESPN is crucial. It is suggested that a small group should be set up to consider these questions. A draft plan to be agreed by the membership should be prepared and the support of the European Commission should be sought for preparation and implementation of the plan. Meanwhile we can develop the twinning links to East European units.

B

HLA AND NON-HLA ANTIBODIES IN RENAL TRANSPLANTATION IN CHILDREN

SPA Rigden and KI Welsh

Antibodies directed against the class I antigens of the MHC arise as a result of previous failed allografts, blood transfusions or pregnancies. In general previously mismatched HLA antigens have been avoided when performing second or subsequent renal transplants in order to prevent early graft loss. However, we believe this policy precludes many recipients from obtaining grafts which would be successful. We have, therefore, adopted the following rules, which have allowed us to successfully transplant many highly sensitised children: 1. regular serum samples are analysed, at dilution, to determine individual specificities of antibodies. 2. only serum samples taken in the previous 6 months are used for the crossmatch. If this is negative, previous specificities which would give a positive cross match are considered: any induced by blood transfusions are ignored but any induced by previous transplants are taken as a bar to transplantation. 3. previous mismatches which have not induced antibodies are allowed. 4. patients being re-transplanted or those who at any time have had panel reactivities of over 50% are given prophylactic ATG.

Further evidence supporting the decision to distinguish antibodies induced by previous transplants from those induced by blood transfusions has come from the study of highly sensitised children receiving recombinant human erythropoietin. In these children: 1. titres never rise unless transfusions or viral infections occur. 2. titres against specificities induced by blood transfusions fall rapidly over 6-12 months. 3. titres against specificities induced by previous mismatches fall much more slowly.

Until the latter part of 1988, our antibody policy was successful with no hyperacute or accelerated rejections and few rejections attributable to antibody. A series of graft losses then occured, antibody mediated on biopsy evidence, but in the total absence of any relevant anti-class I antibody prior to the graft losses. Analysis for laminin, ANCA, Ii, class II MHC and endothelial/monocyte antibodies also failed to determine the cause of the problem. Further analysis showed however, the common presence of an antibody reactive against epithelial cells. This antibody was invariably IgM and its association with graft loss has now been confirmed by others. To date we have lost 19 grafts in the last 2 years, 14 of which have been IgM anti-epithelial cell antibody associated with characteristic biopsy appearances. The cause of this antibody is under intensive investigation.

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C 20

C

TREATMENT OF CORTICOSTEROID RESISTENT ACUTE REJECTION

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The introduction of Cyclosporin A (CsA) for post-transplant immunosuppression has improved patient and graft survival rates. However, reported results in pediatric patients have been variable and often inferior to results obtained in adult patients.
Graft function is endangered by severe or repeated rejection episodes especially in children, who may be more immunologically reactive than adults and whose CsA metabolism is highly variable. In the majority of cases, a three to six days course of 10mg/kg/day prednisolone may be effective in completely reversing rejection crisis. If serum creatinine fails to return to baseline or continues to worsen after 3 pulses of prednisolone or if a rejection occures within one or two weeks after the last rejection treatment it is called steroid resistant rejection.
A thorough understanding in the cellular and molecular events involved in the rejection of transplants has aided designs of new immunosuppressive therapies, i.e. plasmapheresis, antilymphocyte globuline (ALG), antithymocyte globuline (ATG), monoclonal antibodies against the CD 3 lymphocyte antigene (OKT-3, BMA 031), IL-2 receptor antibodies and FK 506.
Attemps to prevent rejection crisis with the prophylactic use of ALG, ATG or OKT-3 have been made, results are not convincing, especially, since a high number of infectious complications has been reported.

In the Hannover experience from 1982 to 1990 14 pediatric renal transplanted patients out 116 were treated with antilymphocyte antibodies. According to our steroid-resistent rejection treatment protocol, ATG (Fresenius) was used in 6 cases, OKT-3 in 9. Basic immunosuppression consisted of CsA and prednisolone in all cases. From 1982 to Nov 1987 all patients received a preoperative loading dosage of CsA (N=74) group A, thereafter, CsA was started 3-6h postoperatively (N=42) group B.
ATG was used from 1982 to 1988 in 6 cases, the dosage was 5 to 7 mg/kg/day given for 5 to 7 days. No patient had serious side effects or infectious complications, 5 responded within 2 to 3 days, 2 patients had a rebound rejection, which could be treated successfully with prednisolone pulses.
Since 1988 OKT-3 was used in 9 cases. While all cases with ATG had biopsy proven rejections, in the cases with OKT-3 biopsies were possible in 6 patients only (3 had an absolute contraindication). In two cases biopsies revealed no rejection: in the first OKT-3 was stopped after 2 days, in the second after 10 days since a HUS was initially misinterpreted as vascular rejection. OKT-3 was given as a short injection 0.1 to 0.2 mg/kg/day for 10 days. A major acute side-effect was a severe bronchospasm in 2 cases. All patients had a rapid improvement of their renal function, usually after 3 days, one after 10 days. Two patients died, the one with 2 OKT-3 injections three months later due to influenca virus pneumonia with consecutive long term artificial ventilation. The other patient died 3 months after OKT-3 therapy due to severe staph. aureus pneumonia and a cytomegalovirus infectious syndrome. Two patient had rebound rejections which responded to prednisolone pulse treatment.
Graft survival rates in group A and B were similar, however, steroid resistent rejections occurred signficanlty less in group A than in group B (4 versus 8, $P<0.01$).
In conclusion, steroid resistent rejections can be treated effectively with the use of antilymphocyte antibodies. However, because of reported deaths under OKT-3, its use should be restricted to cases with biopsy proven steroid-resistent rejection, and it must be used with all precautions including antiviral therapy. Importantly, the basic immunosuppressive protocol may have a significant influence on the occurrence of steroid resistant rejection.

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D

GRAFT VASCULAR THROMBOSIS, A MAJOR CAUSE OF EARLY FAILURE IN PEDIATRIC KIDNEY TRANSPLANTATION (KT), IS PREVENTED BY LOW MOLECULAR WEIGHT HEPARIN.

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From Jan. 1973 to Dec. 1988, 652 consecutive KT were performed in our institution in 585 children and adolescents.
There were 54 early failures within the first 2 months.
Histological examination of the removed graft showed that 30 failures were related to thrombosis of the main vessels : 18 of the renal artery (RA) and 12 of the renal vein (RV). The main risk factor for RA or RV thrombosis was the age of donor : 30% of the 33 grafts performed with a donor less than 2 years and 12% of the 34 grafts performed with a donor of 3 to 5 years ended by vascular thrombosis versus 2.5% of the 440 grafts performed with a donor older than 15. Other risk factors were also identified : age of recipient less than 5, multiple arteries, coagulation abnormalities with history of multiple fistula thrombosis, repeat surgery after grafting for urinary leak or other reason. In addition, acute vascular rejection was suspected on clinical basis in several cases of RA thrombosis but was not possible to confirm by histological examination including immunofluorescence studies. Other risk factors were also identified for RV thrombosis : malformation of vena cava, bench surgery of the renal vein and large adult kidney in small children.
In order to prevent these complications an open prospective study with low molecular weight heparin, Lovenox®(L), was started in Jan. 1989 in recipients at risk of thrombosis, i.e. : 1. donor age less than 10 years ; 2. recipient age less than 5 years ; 3. multiple arteries of graft ; 4. bench surgery or intimal lesions of vessels ; 5. history of repeat fistula thrombosis and/or documented hypercoagulability ; 6. history of previous RA or RV graft thrombosis ; 7. hemoglobin level$>$ 10 g/l in patients receiving erythropoïetin ; 8. L was also given secondarily in case of repeat surgery (excepted for bleeding complication) and in case of suspected acute vascular rejection. The first dose of L was administrated starting 24 hours after surgery in the absence of any obvious persisting bleeding at a dose of 0.4 mg/kg every 12 hours during 21 days. The dose was adjusted on anti Xa activity aiming a peak activity around 0.4 and a residual activity around 0.2. Sixty two patients were grafted during the year 1989 and 42 at risk of thrombosis received preventive L. The 73 patients grafted during the year 1988 with the same immunosuppressive treatment served as control group. The proportion of risk factors was similar in both series (23% of donor less than 5 years in 1988 and in 1989). During the year 1988, 9 out of 73 grafts were lost from RA or RV thrombosis compared to only 1 out of 62 grafts during the year 1989 after starting the preventive L protocol. Side effects of L consisted in bleeding complications in 12 patients, of whom 7 needed blood transfusion. No patient died or lost the graft from bleeding.
In conclusion, this study shows that preventive use of L in KT with risk factors seems to be useful for avoiding vascular thrombosis of the graft, a major cause of early failure especially when using organs harvested in young donors.

F

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Abnormalities in Ion Transport Systems in Hereditary Forms of Hypertension

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Essential hypertension is caused by interaction of the environment with each individual's genetic background. It is common knowledge that hypertensive patients are not all alike (some respond to specific antihypertensive treatments that are totally ineffective in others and vice versa; some have patterns of renal function, body fluid handling or hormonal levels that are different from others) and this together with the finding that different strains of genetically hypertensive rats become hypertensive through different pathogenetic mechanisms, suggest that also in humans there are different forms of the disease, each determined by different, probably independent, primary genetic alterations. The problem is to identify each of these different genetic abnormalities. So far, by measuring only the final phenotype "high blood pressure", numerous family studies have not been able to clarify the pattern of inheritance of hypertension. Following an alternative approach, we are trying to find candidate genes responsible for the pathogenesis of some subtypes of essential hypertension through the identification of intermediate phenotypes that display Mendelian inheritance and could explain some peculiar pathophysiological findings in hypertension. Due to its complexity, studies on the genetic mechanism of human hypertension require experimental and theoretical basis in animal models. The problem is further complicated since it is not known which gene(s) is involved in the production of an intermediate phenotype important for the development of hypertension.

MHS rats develop a spontaneous form of hypertension through an intrinsic kidney abnormality that produces increased tubular sodium resorption in comparison to the normotensive control strain, MNS. Several phenotypic differences between MHS and MNS have been observed. The findings are consistent with the hypothesis of a primary, genetically determined increase of Na-K cotransport across the cell membrane, and since the erythrocyte mirrored very closely the differences found at the kidney tubular cell level, most studies were first performed in red blood cells. The intermediate phenotypes that cosegregated with hypertension in the F_2 generation were: increased erythrocyte Na-K cotransport, reduced erythrocyte volume and sodium concentration. Cross-immunization experiments of erythrocyte cytoskeleton extracts showed an immunochemical difference between MHS and MNS for a 105 KD membrane skeleton protein, adducine. Using this antibody a portion of the adducine gene has been cloned from a mouse spleen cDNA library. In the portion of adducine gene so far cloned a polymorphism between MHS and MNS due to a point mutation was detected. Whereas MHS are all homozygous for the "mutant allele", MNS may be either homozygous for the "normal" allele, heterozygous or homozygous for the "mutant" allele. The heterozygous MNS, though normotensive, have slightly but significantly lower blood pressure than the other MNS. This observation is in line with the hypothesis that selection for lower blood pressure is responsible for the persistent heterozygosity in the MNS strain. It is not yet known whether this mutation affects the ion transport systems.

As in rats, also in humans the search for intermediate phenotypes was greatly stimulated by the discovery that some ouabain resistant sodium transport systems across the erythrocyte membrane are altered in established hypertensives as well as in some normotensive offspring of hypertensive parents. Na-K cotransport and Li-Na countertransport are faster in essential hypertensives compared to normotensive subjects, although the phenotypic means are not greatly different and great overlaps among the distributions are found when large surveys are performed. Both Li-Na countertransport and Na-K cotransport are under genetic control. Studies of these transport systems are important because their increase is associated with increased proximal sodium resorption, a pattern of kidney function that may be responsible for some forms of human essential hypertension.

By maximum likelihood methods in a large set of adult untreated essential hypertensive patients we found that Na-K cotransport was distributed bimodally in hypertensives and unimodally in normotensives. The first mode had a phenotypic value similar to that of the normotensives and comprised 72% of the hypertensives, whereas in the second one the phenotypic value was double and comprises the remaining 27%. Taking the nadir of the distribution of Na-K cotransport values as an arbitrary dividing point, the hypertensives of the high mode were similar to those of the normal mode and to the normotensive controls in many variables (blood pressure, sex distribution, serum creatinine and electrolytes, urinary electrolytes and urinary aldosterone), but had lower plasma renin activity and faster fractional resorption of uric acid. These data indicate that the "high Na-K cotransport hypertensives" are a subgroup of patients with a peculiar pathogenetic mechanism, similar to that of MHS rats, and characterized by increased proximal tubular resorption.

G

Mechanical factors in the development of glomerular damages

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The pathogenetic mechanisms underlying the progressive nature of chronic renal failure are not fully understood. Multiple factors are probably involved. This presentation will analyze the possible role of mechanical factors in the development of glomerular damages characteristic for the progression to glomerular sclerosis.

Expansion of the glomerular mesangium is one of the pathologic hallmarks in this process. Glomerular capillaries and the mesangium together are located in a common compartment bounded by a common basement membrane. Because a hydraulic barrier is not established at the capillary - mesangium interface, it may readily be suggested that the hydraulic pressures in glomerular capillaries and the mesangial interstitium are of similar magnitude. These high pressures in the center of the glomerular tuft have to be counteracted. The countless connections of the GBM to the contractile apparatus of mesangial cells are the structural equivalent of this requirement.

Structural studies (LM, TEM, SEM) designed to induce mesangial expansion in the rat (acute and chronic glomerular hyperperfusion models, Habu venom mesangiolysis) suggest that (a) mesangial cell/GBM connections are the most important structures stabilizing the mesangium against mesangial expansion, (b) local disruption of mesangial cell/GBM connection seem to be an early event in the development of mesangial expansion, (c) juxtacapillary and axial mesangial cell/GBM connections have different susceptibilities to such disruptions resulting in the fact that mesangial expansion is a frequent, formation of microaneurysms a rare event, and (d) that the characteristics of chronic mesangial expansion (hypercellularity, hypertrophy of mesangial cells, accumulation of mesangial matrix) can be regarded as processes to repair disruptions of mesangial cell/GBM connections.

Characteristic changes of podocytes (retraction of foot processes, attenuation of major processes, development of pseudocysts) appaear to be the consequence of increased mechanical stress developing on the basis of glomerular hypertrophy or of mesangial expansion (or on the basis of both). Podocytes have lost their ability to multiply by mitotic division. Thus, when the tuft hypertrophies a fixed number of podocytes have to service a considerably enlarged capillary surface (number and diameter of capillaries are increased); podocytes obviously cannot keep up with the capillary hypertrophy. The distances between capillary surfaces belonging to a certain podocyte increase dramatically. In consequence the podocyte processes are exposed to increased tension, they are stretched out and become attenuated, finally they retract or are disrupted.

A similar progression may develop on the basis of mesangial expansion. Capillary loops serviced by a certain podocyte are moved away from each other by the expanding mesangium forcing the podocyte to span much larger distances than before. Again, the capacity to an adaptive hypertrophy is obviously limited, similar structural damages are encountered as described above.

Taken together, the structural integrity of the tuft is maintained by the mesangial cell/GBM connections counteracting the high hydraulic pressure within the center of the glomerular tuft. Damage to these connections will results in mesangial expansion. Enlargement of the tuft (either locally by mesangial expansion, or in total by hypertrophy) represents a challenge to the fixed number of podocytes, whose ability to adaptive hypertrophy is obviously limited.

H

RENAL TUBULAR CHLORIDE TRANSPORT

R. Greger

The normal kidney filters some 23 mol Cl^- per day. The urinary excretion is around 1 % of this amount. 99 % of the filtered load are reabsorbed along the various nephron segments. The proximal tubule (PT) reclaims some 50-60 %, the thick ascending limb of the loop of Henle (TAL) reabsorbs 20-30 %, the distal tubule (DT) reabsorbs some 5-10%, and the remaining few % are reclaimed in the collecting tubule (CT). The mechanisms of reabsorption are heterogenous.

In the PT the vast majority of the reabsorption occurs paracellularly, i.e. between the cells through the tight juntions and lateral spaces. The driving forces are provided by the preferential transcellular HCO_3^- reabsorption through the PT cell and by the water flux (solvent drag). This mode of reabsorption is highly economical, but it prevents the build up of seizable concentration gradients across the tubule epithelium. Little Cl^- crosses the PT cell. This moiety of Cl^- reabsorption utilizes a Cl^-/formate anion exchange system in the luminal membrane and some other anion transporter in the basolateral membrane. No specific inhibitor of Cl^- reabsorption in the proximal tubule is known. Cl^- reabsorption in this nephron segment is reduced by inhibitors of HCO_3^- reabsorption such as acetazolamide and thiazides. These inhibitors of carbonic anhydrase reduce the reabsorption of HCO_3^- and hence the passive reabsorption of Cl^-. The tubule fluid leaving the PT has a mean Cl^- concentration of 150 mmol/l, it represents approximately 50-60 % of the filtered load.

Cl^- transport in the thin limbs of the loop of Henle is probably entirely passive. Some 30 % of the filtered load are delivered to the TAL. The TAL segment reabsobs Cl^- secondarly actively. All reabsorption occurs across the TAL cells. This reabsorption of Na^+ and Cl^- is the key mechanism for the counter current multiplier, and is, therefore, equally responsible for the ability of the kidney to produce a highly concentrated urine (in the presence of antidiuretic hormone = ADH) and a diluted urine in water diuresis. This nephron segment reabsorbs some 20-30 % of the filtered load. The Cl^- concentration leaving this nephron segment is around 20-40 mmol/l. By the beginning of the DT only some 10 % of the filtered load of Cl^- are recovered. The reabsorptive mechanism in the TAL involves the coupled uptake of Cl^- with Na^+ and K^+ by the so-called $Na^+2Cl^-K^+$ cotransport system Na^+ is removed from the cell on the blood side by the $(Na^+{+}K^+)$-ATPase. The K^+ taken up across the luminal membrane recycles back into the lumen through K^+ channels in this membrane. Cl^- leaves the cell across the basolateral membrane via Cl^- channels and via a KCl cotransport system The conductance properties of this nephron segment are reponsible for the generation of a lumen positive voltage. This voltage drives part (some 50%) of the reabsorbed Na^+ between the cells through the tight junctions and the lateral spaces. One can calculate that 1 mol ATP consumed by the basolateral $(Na^+{+}K^+)$-ATPase in the TAL segment pays for as much as 6 mols NaCl reabsorbed by this mechanism. This is highly relevant since the rates of transport in the TAL are large and the supply with fuels and O_2 is borderline. The $Na^+2Cl^-K^+$ cotransporter is inhibited reversibly by loop diuretics such as furosemide. This leads to an immediate inhibition of NaCl reabsorption in TAL cells.

The macula densa cells have properties which are identical to that of TAL cells. This explains why loop diuretics interrupt the feedback mechanism, i.e. they prevent a fall in single nephron filtration rate, which otherwise would have to occur as soon as the NaCl concentration, leaving the TAL segment and sensed by the macula densa cells, increases.

The DT reabsorbs some 5-10 % of the filtered Cl^-. Recent preliminary evidence indicates that this reabsorption occurs across the DT cells. Cl^- is taken up across the luminal membrane via a Na^+Cl^- cotransport system, and Na^+ is removed from the cell by the basolateral $(Na^+{+}K^+)$-ATPase. The luminal Na^+Cl^- cotransporter is inhibited by thiazide diuretics. The Cl^- concentration leaving the DT is around 50-100 mmol/l. The amount of Cl^- entering the CT is a few percent of that filtered. The mechanisms of Cl^- reabsorption in the CT are unknown. It has been shown that Cl^- does not cross the (Na^+ reabsorbing and K^+ secreting) principal cell. Hence, by exclusion, Cl^- is thought to move between the cells or across the intercalated A- or B-cells.

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I

FAMILIAL HYPOKALAEMIA-HYPOMAGNESAEMIA (GITELMAN'S SYNDROME)

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Nosology. The syndrome of familial hypokalemia-hypomagnesaemia was first described in 3 female siblings by Gitelman et al in 1966 (1). This entity, inherited as a recessive trait, is frequently confused with classic Bartter's syndrome, specially in the adult literature. Similar biochemical findings may be observed after treatment with cisplatin (2).

Clinical and biochemical data (3). Patients with Gitelman's syndrome are often asymptomatic, with the exception of transient episodes of weakness and tetany, which are usually accompanied by abdominal pain, vomiting and fever. Polyuria and growth retardation are absent. The disease-free intervals are variable and in many cases the diagnosis is only made when patient reaches adulthood.

The outstanding biochemical feature is hypomagnesaemia. Hypokalaemia and moderate metabolic alkalosis are usually but not obligatorily present. A modest elevation in plasma uric acid may be observed, although in the whole renal function is normal. Hyperreninism, hyperaldosteronism and hyperprostaglandinism contribute to the confusion with Bartter's syndrome. No abnormal findings are present at the renal biopsy, although hypertrophy of juxtaglomerular apparatus may be exceptionally present. The most characteristic urinary finding, besides hypermagnesiuria and hyperkaliuria, is the striking diminution of urinary calcium excretion. The study of distal tubular function reveals normal concentrating and acidifying mechanisms but moderately reduced distal fractional NaCl reabsorption during hypotonic saline diuresis. Study of Mg reabsorption during $MgSO_4$ infusion indicates that overall Mg reabsorption is normal but renal Mg threshold is diminished.

Pathogenesis. The dissociation of renal Ca and Mg transport, the moderate degree of Na, Cl and K wasting and the low renal Mg threshold with a normal Mg Tm, all point to the presence of a hereditary defect in the distal convoluted tubule, which in many ways resembles the effect of chronic administration of a thiazide diuretic. We tried to demonstrate this hypothesis by studying segmental NaCl reabsorption during water diuresis. This can be done by calculation of free water clearance (C_{H_2O}) before and after acute frusemide (F) administration (4). With this protocol estimates can be made of: free water back-diffusion (C_{H_2O}-BD = VF-V); total volume of free water formed (C_{H_2O}-T = C_{H_2O} + C_{H_2O}-BD); volume of free water formed by distal convoluted tubule (C_{H_2O}-DT = C_{H_2O}-F); volume of free water formed by Henle's loop (C_{H_2O}-HL = C_{H_2O}-T - C_{H_2O}-DT); distal NaCl delivery (C_{H_2O}-T + C_{Cl}); percent of distal NaCl delivery totally reabsorbed by distal segments (C_{H_2O}-T/C_{H_2O}-T + C_{Cl}); percent of distal NaCl delivery reabsorbed by distal convoluted tubule (C_{H_2O}-DT/C_{H_2O}-T + C_{Cl}); and percent of distal NaCl delivery reabsorbed by Henle's loop (C_{H_2O}-HL/C_{H_2O}-T + C_{Cl}).

We applied this test to 5 patients with Gitelman's syndrome (mean age: 14.7 y) and 4 control children (mean age: 12.0 y).

	Gitelman	Control	p
C_{H_2O}-T (ml/dl GF)	10.5 ± 1.0	17.4 ± 3.9	<0.05
C_{H_2O}-DT (ml/dl GF)	2.9 ± 0.5	5.4 ± 0.9	<0.01
C_{H_2O}-HL (ml/dl GF)	7.6 ± 0.9	12.0 ± 3.3	NS
C_{H_2O}-T + C_{Cl} (ml/dl GF)	11.9 ± 0.9	18.4 ± 4.2	<0.05
C_{H_2O}-T/C_{H_2O}-T + C_{Cl}	0.89± 0.04	0.95± 0.02	<0.05
C_{H_2O}-DT/C_{H_2O}-T + C_{Cl}	0.25± 0.03	0.30± 0.05	NS
C_{H_2O}-HL/C_{H_2O}-T + C_{Cl}	0.64± 0.07	0.65± 0.05	NS

A significant finding in Gitelman's syndrome was the blunted calciuric response to frusemide (U_{Ca}/U_{Cr}: 0.56 vs 1.54, $p<0.001$) These data support the hypothesis that Gitelman's syndrome represents a defect in the distal tubule, while Bartter's syndrome may represent a defect in ascending loop of Henle.

Therapy. The patients are best treated with $MgCl_2$, although in severe cases potassium salts and prostaglandin inhibitors are also needed.

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J

BARTTER SYNDROME : THE NEONATAL VARIANT WITH HYPERCALCIURIA

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We studied 7 patients with the neonatal variant of Bartter syndrome. They all have in common the following features :
- prenatal onset with polyhydramnios
- causing premature delivery
- marked polyuria after birth with
- severe renal sodiumchloride loss
- which turns into renal potassium losing later on
- hypercalciuria from the beginning
- leading to nephrocalcinosis and
- associated with elevated serum PTH levels
- and high 1,25 diOH D levels
- indomethacin only partially corrects most abnormalities.

POLYHYDRAMNIOS was diagnosed from the 20th week of gestation on. One to multiple amniocenteses were performed. Unsuppressable premature labour led to delivery at a gestational age of 27 to 33 weeks. Amniotic fluid has been analysed in 5 cases. Sodium, potassium, calcium and creatinine concentrations were within normal ranges. Chloride levels however were 2 SD above the mean normal values. THIS FINDING ALLOWS FOR PRENATAL DIAGNOSIS OF BARTTER SYNDROME IN CASES OF POLYHYDRAMNIOS. Prostaglandins E2 and F2a were low but in the normal range when the diluting factor is taken into account.
Polyhydramnios was shown to be the consequence of intrauterine polyuria. In patient I.W. fetal diuresis at 28 weeks was 38 ml/h i.e. 912 ml/24h.

Postnatal POLYURIA is impressive. Maximal urine volumes were between 14 and 20 ml/kg per h. In two patients 24 h urine volume exceeded body weight. The composition of this urine is most remarkable : it contains tremendous amounts of Na and Cl (up to 125 mmol/l) and relatively small amounts of K (less than 10 mmol/l). This NaCl-WASTING is temporary. Gradually urinary K concentrations raise, equal and finally, 6 to 12 weeks after birth, exceed Na concentrations. From that moment on the real Bartter situation is established with HYPOKALEMIA and HYPERKALIURIA. By that time urine volumes have dropped quite importantly : polyuria is still present with a urine output of about 6 to 10 ml/kg per h.

Urinary PROSTAGLANDIN E2 concentrations (UPGE2) are within the normal range in the first samples obtained after birth. In patient I.W. (who lost 14 % of BW within 3 days) a most striking increase in UPGE2 up to twenty fold was documented in the first days. In patient E.D. with a weight loss of 7.5 % the increase in UPGE2 was much less. In patient R.V. who, thanks to optimal fluid and electrolyte management only lost 5 % of BW, no increase of UPGE2 levels at all was seen. The sample applies to plasma renine activity (PRA) and plasma aldosterone concentrations (PAC) : at birth, PRA and PAC are within normal ranges; with appropriate fluid and electrolyte therapy the figures remain within normal ranges.

HYPERCALCIURIA is a feature present from birth. First urine samples after birth have high calcium content : urinary calcium/creatinine ratios (UCa/Cr) are between 3.1 and 8.6 (mg/mg). As long as the NaCl losing persists very high urinary Ca concentrations are found. Later on when K-losing is predominant, hypercalciuria persists be it to a lesser degree (UCa/Cr about 1.0). NEPHROCALCINOSIS has been documented in all patients. In one patient renal hyperechogenicity was documented at the age of 6 weeks. Serum ionised Ca is rather low. Serum PTH levels as well as serum 1,25 diOH Vit D levels are elevated. These findings are consistent with a renal origin of hypercalciuria.

TREATMENT of patients with this severe form of bartter syndrome is not easy. In the early weeks, tremendous amounts of fluid with high NaCl contents must be administered i.v. Later on extra fluid and K supplements are necessary to maintain a decent electrolyte status and to make the children grow. Spironolactone is of appreciable help in improving K balance but it increases UCa. INDOMETHACIN therapy (1.5 to 2.5 mg/kg per day) normalizes UPGE2, PRA and PAC but only partially corrects hypokalemic alkalosis, polyuria and hypercalciuria.
Different therapies were tried to further reduce UCa. (1) With Indomethacin doses above 2.5 mg/kg per day GRF dropped. (2) Potassiumphosphate (K up to 30 mg/kg per day) did not significantly reduce UCa. (3) Neither dietary Ca reduction nor Ca supplementation improved hypercalciuria.

(4) Amiloride had an equivocal effect in one patient and slightly reduced the hypercalciuria in another.

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K

BARTTER'S SYNDROME - WHAT IT IS AND WHAT IT ISN'T

M J Dillon

In 1962 Bartter and coworkers described a new syndrome of growth and mental retardation, hypokalaemic alkalosis, increased aldosterone secretion rate and plasma angiotensin II concentration in the presence of a normal blood pressure, juxta glomerular cell hyperplasia, pitressin resistant hyposthenuria and decreased pressor responsiveness to infused angiotensin II. Many reports subsequently appeared describing a spectrum of clinical and biochemical features considered to be manifestations of the condition causing some difficulty in identifying criteria for diagnosis. For the diagnosis to be seriously considered the following must be present: hypokalaemia, hypochloraemia, alkalosis, hyperreninaemia, normotension, elevated urine potassium and chloride excretion in the absence of other conditions that might cause similar features.

In addition to these basic components a number of other findings have been described. Some of these are probably essential aspects of Bartter's syndrome and help in understanding the pathophysiology of the condition; others may serve to distinguish between the "classic" syndrome and "Bartter-like" disorders; still others are just epiphenomena. The major elements are defective renal tubular handling of sodium and potassium, abnormal chloride reabsorption in the ascending limb of the loop of Henle, abnormal intracellular electrolyte concentrations in erythrocytes and muscle cells and abnormal membrane sodium and potassium transport. Other reported features include: hypercalcaemia, hypercalciuria, hypophosphataemia, hypomagnesaemia, hypermagnesuria, defective renal tubular acidification, excess renal prostaglandin production, abnormalities of the kallikrein-kinin system, nephrocalcinosis, decreased renal function and rickets. However, patients manifesting features listed within this latter group may well be those in whom the diagnosis is not Bartter's syndrome but a "Bartter-like" syndrome such as familial hypokalaemia-hypomagnesaemia, incomplete distal renal tubular acidosis or some form of Fanconi syndrome. Attempts have also been made to distinguish an hyperprostaglandin E syndrome with hypokalaemia and hypercalciuria from Bartter's syndrome but this remains contraversial.

On the other hand there are a number of so called "pseudo-Bartter" syndromes including those associated with laxative abuse, cyclical vomiting, pyloric stenosis, chloride deficient diets, congenital chloridorrhoea, and cystic fibrosis that have a conspicuous lack of chloride in the urine. The exception to this rule is loop diuretic abuse that mimics Bartter's syndrome very closely.

The diagnosis of Bartter's syndrome is still one of exclusion but in recent years a degree of specificity has been applied to certain biochemical investigations which has been enhanced by the greater understanding of the role of renal tubular handling of chloride and the disturbances of membrane electrolyte transport in its pathophysiology.

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C 24

L

STRATEGIES FOR TREATMENT OF RENAL GROWTH FAILURE: THE IMPACT OF GROWTH HORMONE THERAPY.

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Serum concentration of growth hormone (GH) is high in uremia because of hypersecretion and/or reduced renal metabolic clearance. Serum concentration of insulin-like growth factor-I (IGF-I) is within the normal range, but IGF-I bioactivity is decreased. Increased circulating GH does not adequately stimulate hepatic IGF-I production, possibly, because of decreased expression of the GH receptor. Within the serum, IGF-I is mainly transported by IGF-binding protein-3 (IGF-BP-3) and to less than 10% by IGF-BP-1. Under normal conditions, total IGF concentration is mainly determined by the concentration of IGF-BP. Hereby, the molar ratio of IGF to IGF-BP is approximately 1:1 because of the rapid clearance of free IGF. In CRF, however, there is an excess of IGF-BP-3 and IGF-BP-1 over total IGF (IGF-I + IGF-II). This results from the reduced renal clearance for small molecular weight subunits of IGF-BP. The excess of IGF-BP-3 leads to a decrease of the biologically active free IGF-I and consequently to a decrease of IGF bioactivity. Exogenous GH can increase the ratio of IGF-I to IGF-BP-3 and by this normalize IGF bioactivity. These findings provide a rationale for the long-term rhGH treatment of children with CRF.
Using a dose regimen of about 4 IU rhGH/m^2/day s.c. has resulted in doubling of the growth rate in prepubertal children with preterminal and terminal renal failure. Height SDS corrected for chronological age increases more than height SDS corrected for bone age. Therefore, it can be expected that the final height of patients will be incrased. The situation for treatment during puberty is not clear to date. Since growth hormone induces early puberty in monkeys and accelerates puberty in GH deficient children, an improvement of final height resulting from rhGH treatment in the prepubertal period could theoretically be lost by early onset of puberty and shortening of duration of puberty. In addition, in many pubertal renal children the improvement of growth rate by rhGH is not as impressive as in prepubertal patients. Consequently, it is possibly the best concept to treat a stunted patient with CRF early before puberty, to bring back his height to his target centile and to stop rhGH treatment before puberty. But it would be wrong to treat uncritically all renal patients with growth problems. Conservative treatment modalities like calorie supplements, phosphate restriction, vitamin D, bicarbonate supplements and adequate fluid and sodium intake must not be forgotten.
RhGH is also able to improve growth in transplanted children on steroid treatment. For slowly growing transplanted patients, the same guidelines should be used with respect to age and puberty as in children before transplantation. Successful renal transplantation is able to induce catch-up growth when no or low dose steroid treatment is given. Therefore, rhGH therapy should not be instituted unless spontaneous growth rate has been followed for one or two years after transplantation. In addition, one has to be aware that the risk of triggering reaction crisis is not completely ruled out yet.

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M

DIETARY FACTORS AND PROGRESSION OF CHRONIC RENAL FAILURE.

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A great deal of interest has recently been focused on the effects of dietary components on renal function. Several Countries have initiated multicentre clinical trials to determine whether long-term restriction of protein and phosphate may retard the decline in renal function in patients with progressive renal disease. I will discuss the following points:

1. THE ADVERSE ROLE OF PROTEIN,PHOSPHATE AND LIPIDS.
The deleterious effects of protein and phosphate on renal structure and function have been observed both in experimental and in clinical studies. High protein and phosphate intakes invariably promote glomerular sclerosis in animals with several models of renal disease. In patients with chronic renal failure (CRF),self-controlled studies have shown that long-term administration of normal to high protein diets increases proteinuria and accelerates the rate of decline in GFR.
Recently,it has been hypothesized that progressive kidney disease may be mediated by abnormalities of lipid metabolism. Clinical support to this hypothesis is provided by preliminary studies suggesting that progression of CRF is accelerated in patients with the nephrotic syndrome. In addition,the rate of progression of CRF may be significantly faster in hyperlipidemic than in normolipidemic patients,regardless of their underlying renal pathology.

2. THE PROTECTIVE EFFECT OF DIETARY INTERVENTION.
After some earlier reports showing positive effects of low protein diets (LPD) on the course of CRF,in the last 8 years several clinical studies on the effects of LPD in patients with CRF have been published. Virtually all these studies have concluded that protein restriction slowed the progression of CRF,and almost all of them have been criticized for beiny retrospective,uncontrolled,or methodologically inadequate.
The validity of well-conducted randomized clinical trials is out of discussion,but it is hampered by too many variables(age, sex,race,underlying renal disease,magnitude of proteinuria, severity of systemic hypertension,degree of functional deterioration,rate of progression before randomization,compliance with LPD) that should be considered when assignement of patients between treated and untreated groups is to be made.
Clinical evidence exists that the natural history of patients with CRF is influenced by conservative treatment,which means not only diet but also administration of pharmacologic agents and accurate clinical check-ups. As to the diet,Nephrologists face three possibilities: the unsupplemented LPD,the essential aminoacid-supplemented diet,and the ketoacid-supplemented diet. The LPD is certainly most suitable for patients with early CRF. In our experience,the earlier the conservative approach the better are the results in terms of survival of renal function. This conclusion is supported by rigorous statistical analysis (multiple regression,Cox's proportional hazard method,actuarial survival probability) applied to large populations of patients.
The ideal diet for patients with early CRF should provide approximately 35 Kcal/Kg,0.6 g/Kg of protein,650 mg of phosphate,and 110 g of lipid,with an elevated P/S fatty acid ratio. The compliance with this dietary regimen is quite satisfactory,at least in Italian patients,and there is no evidence of malnutrition even after years of follow-up.
Clearly,LPD should be regarded as a part of the conservative treatment of CRF. Clinical evidence exists,however,that a moderate restriction of protein and phosphate and an adequate manipulation of dietary lipids are the ground above which the other components of conservative treatment in patients with CRF may be built up.

N

BIOLOGY OF NORMAL AND COMPENSATORY RENAL GROWTH

Leon G. Fine

Where renal growth occurs over a long period without preceding loss of cells, this is accomplished by a process of hypertrophy (cell enlargement) which allows each component part of the nephron to increase in size while maintaining a normal architecture. Where cell death occurs e.g., following ischemic or toxic injury, regenerative hyperplasia occurs only in those areas where the integrity of the nephron has been lost. Finally, in all situations involving tubular hypertrophy or hyperplasia, renal interstitial cells lay down extracellular matrix and, where this is exaggerated or perturbed, tubulointerstitial disease may result.

a) Tubular Hypertrophy. Hypertrophy following loss of nephrons involves all parts of the nephron. Glomerular hypertrophy occurs in the remnant kidney and in those nephrons which are relatively spared in glomerulonephritis. Correlations suggest that larger glomeruli are more susceptible to the development of sclerosis, but the nature of the enlargement (hypertrophy vs. hyperplasia) and the cell types involved have not been elucidated. Tubular hypertrophy is closely linked to glomerular hyperfunction. Early events in hypertrophy include a rise in GFR, renal plasma flow, Na^+H^+ exchange, Na^+-K^+ ATPase activity and increased ammoniagenesis. One or more of these could trigger the growth process, but cause-and-effect relationships have not been established. Enlargement of the tubular cell proceeds by a route which is different from the enlargement which all cells undergo prior to cell division. Thus, in an in vivo model of renal regeneration there is early activation of oncogenes and genes encoding for structural and transport proteins, whereas no such activation occurs following uninephrectomy. In regenerative hyperplasia and in models of differentiation, a family of primary response genes is induced, some of which encode for transcription factors. No such induction occurs in hypertrophy. The only genes which have been shown to be transcriptionally activated are those which encode for ribosomal RNA. Thus, the regulation of the growth process in hypertrophy is fundamentally different from that which occurs in hyperplasia and differentiation. There is no evidence as yet to implicate one or more growth factors in the process.

b) Tubular Regeneration. Tubular regeneration occurs after acute tubular necrosis (ATN). A potent mitogen for renal tubular cells is epidermal growth factor (EGF) which is produced by the kidney. Although EGF precursor mRNA decreases after ATN, up-regulation of EGF receptors occurs on the viable cells and when exogenous EGF is administered, functional recovery is accelerated.

c) Interstitial Fibroblast Growth. Renal hypertrophy involves an increase in extracellular matrix production that also occurs in tubulo-interstitial diseases and as a concomitant of glomerular diseases. Interstitial fibroblast function must be perturbed in these disease states. Preliminary in vitro studies have shown differences between cortical (CF) and papillary fibroblasts (PF) in the rabbit, with the latter having a more rapid turnover rate. PF show a marked mitogenic response to PDGF whereas CF do not. Medullary collecting duct cells (MCD) produced PDGF and express c-sis (ß chain) in vitro. They release a factor which stimulates mitogenesis of papillary fibroblasts and which is inhibited by anti-PDGF antibody. Hence a local PDGF-dependent paracrine system exists in the inner medulla. Other regions of the kidney may employ other growth factor-dependent systems to regulate interstitial function.

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O

AGE DEPENDENCE OF COMPENSATORY RENAL GROWTH

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When renal parenchyma is lost, the remaining nephrons respond by increasing their functional capacity. During this compensatory renal growth (CRG) the glomerulus and the tubule undergo parallel functional adaptations and thus the glomerulo-tubular balance is usually preserved. Provided that no more than 50% of total renal parenchyma is lost, the capacity to excrete solutes and to maintain salt and water homoeostasis can be fully maintained. The compensatory response to nephron loss might however be associated with precocious development of focal glomerulosclerosis (FGS).

The mechanisms by which the nephrons adapt to loss of renal parenchyma are age-dependent. CRG continues for a longer period when starting in infancy than when starting in adulthood. Consequentially, renal size and GFR increase to a higher extent in the infant remnant kidney. In animals nephrectomized (nx) in infancy, the remnant kidney's weight and GFR increase about 100% within 7-8 weeks. In adult nx animals, the maximal renal enlargement (60-70%) is achieved within 2-3 weeks after surgery. Studies in adult organ donors and in children with single kidney have demonstrated a similar response. Both the glomerulus and the tubule enlarge to a higher extent in the infant than in the adult remnant kidney. Tissue growth can be achieved by enlargement of pre-existing cells or by formation of additional ones. The contribution of cellular hypertrophy and cellular hyperplasia has been studied in some details in the proximal tubule segment. While kidney CRG in adulthood is sustained mainly by cellular hypertrophy, in infancy only hyperplasia seems to contribute to CRG.

In adulthood, the hyperfiltration that characterizes CRG appears to be due mainly, if not only, to an increased ultrafiltration pressure. The glomerular hemodynamic changes occurring after nx in infancy differ from those occurring after surgery in adulthood. The infant remnant glomerulus is characterized by an immediate increase in ultrafiltration pressure, a slow but remarkable increase in filtration area and a decrease in hydraulic conductivity. The increase in ultrafiltration pressure however does not seem to be essential for hyperfiltration following infant nx, since chronic treatment with a calcium channel blocker abolished glomerular hypertension but did not affect CRG nor hyperfiltration.

Since the glomerulo-tubular balance is preserved during CRG, glomerular hyperfiltration is associated with increased tubular Na reabsorption rate. In the infant remnant kidney, the length of the proximal convoluted tubule is two-fold increased. This increase is due to the high degree of cellular hyperplasia. The NaKATPase is the key enzyme for active Na reabsorption through tubular cells. In the proximal convoluted tubule the enzyme density per unity of length increase in the adult remnant kidney. In the infant remnant kidney no increase in enzyme density per unit of length can be recorded.

CRG starting in infancy might be associated with a higher risk for developing FGS. Autoptic case reports have shown that FGS might develop precociously in single kidney since infancy. Long-term follow-up studies in animals and in humans seem to indicate that CRG in infancy is associated with a higher albumin excretion rate and a higher incidence of FGS.

In summary the infant kidney has a higher capacity for CRG than the adult one. There are several differences in the biological adaptation of the glomerular and the tubular cells. Knowledge about these age dependent compensatory mechanisms will give us informations about the principles for normal growth and about the factors that might predispose to FGS.

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P

LONG-TERM RENAL FUNCTION AFTER UNILATERAL NEPHRECTOMY IN CHILDHOOD.

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With the development by Brenner and collegues of the theory of glomerular hyperfiltration and hypertension after removal of renal mass in rats, the long-term functional outcome of unilateral nephrectomy (UN) in humans has received much attention. The knowledge that a single kidney was compatible with life was already known by Aristotle. Since elective UN has become a common surgical procedure, the fate of the remaining kidney has been an object of concern. About 50 years ago papers have been published like "The future of the unilaterally nephrectomized patient" and "Life after nephrectomy". Translated into the pediatric clinic, the questions asked were: 'Can my child live with one kidney?' 'Will it shorten its life?' and 'Will the removal of one kidney handicap my child and limit its activities?' Fifty years ago, the answer was yes to the first and no to the second question. The answer to the third was also no if certain precautions were taken. What do we know by now?

In the 1980's there has been a revival to study the long-term consequences of having only one kidney. Best studied are the kidney donors. Recently, 25 studies have been reviewed [Fotino, Am JKid Dis, 13:88, 1989]. The GFR augments to a level of 70-85% of the normal two-kidney GFR and a stable state of hyperfiltration is maintained up to 20-25 years after kidney donation.

In children, however, UN is performed at a much younger age. From experimental work it has become clear that the age at nephrectomy may be a risk factor in developing renal damage in the remainng kidney. Clinically this can be studied in two situations: unilateral renal agenesis (URA) and UN for acquired unilateral disease. In URA isolated case reports have suggested an increased incidence of focal glomerulosclerosis and progressive renal insufficiency. However, only a large prospective long-term study can establish whether URA by itself is a significant risk factor for loss of renal function that can be attributed solely to chronic hyperfiltration.

UN for congenital or acquired disease is frequently performed in childhood. The long-term effects have been reported in a study by Robitaille et al. (n=27) [Lancet, i:1297, 1985] and two studies by Wikstad et al. (I. n=37 for Wilms' tumor and hydronephrosis) [Acta Paediatr Scand, 75:408, 1986], (II. n=21 plus 15 cases of URA) [Ped Nephrol, 2:177, 1988]. Robitaille et al., assessing Creatinine-clearance (C-Cr), proteinuria, and blood pressure, concluded that mean renal function was good. Neither the age at the time of nephrectomy (1 mo-12 yr), nor the duration of the follow-up (17-33 yr), nor sex had an influence on the residual C-Cr.

Wikstad et al. determined the GFR, as Inulin clearance (C-In), albuminuria and blood pressure. From the first study they conluded that 'The GFR did not seem to decline with a longer follow-up time (5-32 yr).' From the second study, with a follow-up of 7-40 yrs, it was concluded that the 'Prognosis is good, but the late decrease in GFR and increase in albumin excretion may indicate a moderate risk for premature renal damage.'

In 1988 we initiated our own study into the long-term follow-up of UN in childhood. A total of about 180 cases of UN were traced and divided in two groups. In Group I, the present age is over 25 yrs with a follow-up of 20-52 yrs. In Group II, the present age is 18-25 yrs, with a follow-up of 8-25 yrs. In both groups we assessed the GFR, C-Cr, proteinuria, and blood pressure. The GFR data of 70 cases could be preliminary analyzed. Only slight differences exist between the mean GFR of groups I and II, which can be explained by the effect of aging on the renal function. However, 11 cases (9 male, 2 female) had a relatively low GFR. Six could be explained by renal alterations already present at the time of UN. Five cases remain unexplained yet, and may need additional follow-up studies.

From the reported studies and our preliminary data we may conclude, that the risk to develop progressive renal damage in children remaining with a single kidney after UN is relatively small. However, some individuals may be at risk to develop chronic renal failure. It remains a challenge to identify those cases and offer them an optimal follow-up after surgery.

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Q

THE MEASUREMENT OF THE RENAL RESERVE AND OF THE TUBULO-GLOMERULAR FEEDBACK MECHANISM IN CHILDHOOD

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The renal hemodynamic response to a meat meal(2g/Kg BW)was studied in 11 healthy children and in 10 children with mean plasma creatinine concentration of 2.6 ± 0.1 mg/dl due to chronic renal failure (CRF) of various etiologies.
In the healthy status, after a meat meal, the glomerular filtration rate (GFR) increased significantly from a baseline value of 119.0 ± 5.0 to a peak of 159 ± 5.8 ml/min/1.73 sq.m.; in CRF baseline GFR averaged 49 ± 4.0 and at peak 76.6 ± 7.2 ml/min/1.73 sq.m. ($p<0.005$). The peak GFR response was reached earlier in healthy subjects than in CRF ($p<0.05$) and did not correlate with age or with baseline GFR. Renal plasma flow (RPF) in healthy controls increased from 532 ± 32 at baseline to 646 ±42.9 ml/min/1.73 sq.m. after the meat meal ($p<0.005$). Also in CRF after a meat meal there was a significant increase in RPF from 278 ± 51 to 65 ± 66 ml/min/1.73 sq.m. ($p<0.005$). The filtration fraction was not affected. The percent increase over baseline values of GFR and RPF at the peak was significantly higher in diseased children. Renal reserve averaged 28.1 ± 5.3 ml/min in diseased children and 39.7 ± 5.2 ml/min ($p<0.01$).Taken as a whole the data indicate that:
(1). a meat meal is a suitable method to recruit renal reserve in normal children and in children with chronic renal failure;
(2). the renal reserve is normal in chronic renal failure with a mean plasma creatinine of 2.6 mg/dl.

Tubular function was measured by lithium clearance (C_{Li}) and by its derived formulae before and after the transient increase (lasting 90 minutes) of Glomerular Filtration Rate (GFR) which followed a meat meal (2 g/Kg B.W:of protein) in 12 normal children. Three baseline and 4 post-meal clearances were obtained each lasting 30 minutes. Mean baseline C_{Li} was 23.1 ±1.64 ml/min/1.73 sq.m. At peak GFR response (60 min from starting the meal) C_{Li} averaged 27.6 ± 2.4 ml/min/1.73 sq.m. ($p<0.025$ vs baseline) and it was further increased (32.2 ± 5.04 ml/min x 1.73 sq.m.,$p<0.01$ vs baseline) 120 minutes after starting the meal while GFR has returned to baseline values. Fractional Lithium Excretion averaged 0.23 ± 0.04 at baseline and increased continuously after the meat meal and at completion of the study it averaged 0.38 ± 0.07 ($p<0.025$ vs baseline). The distal absolute and fractional sodium reabsorption increased throughout the postmeal studies and peaked at 120 minutes.
The functional changes were associated with statistically-significant increase in the postmeal plasma concentration of insulin, glucagon, and of total amino acids. The latter at the end of the study had been almost doubled 5600 ± 780 uM/L versus 3200 uM/L at baseline, ($p<0.01$). The data indicate that the Tubulo-Glomerular Feedback Mechanism operates normally after a meat meal. The finding on increased distal sodium reabsorption might point to the existence of an insulin dependent mechanism.

S

ROLE OF ENDOTHELIN (ET) IN THE PROGRESSION OF RENAL DISEASE.

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Numerous studies in the last decade have set out to clarify the process of progressive deterioration of renal function that occurs in animals and humans after a critical reduction in the number of nephron units either by surgical ablation or by various diseases. The recently described peptide of endothelial origin, endothelin, in addition to being a potent vasoconstrictor, also functions as a mitogen of mesangial cells and could play a major role in the progression of renal disease to glomerulosclerosis.
We investigated renal ET production in rats with renal mass ablation (RMR) a model of progressive renal disease characterized by glomerular hemodynamic alterations and capillary thrombosis, and in sham-operated (S) animals. Homogenates of renal cortical tissue from RMR rats incubated with 2.5 U/ml thrombin for 24 h, 45 but not 7 days after surgery, generated significant ($p<0.01$) more ET than cortex from S (7 days: RMR 0.50±0.35 vs S 0.24±0.12; 45 days: RMR 2.87±1.80 vs S 0.34±0.19 pg/mg/protein/24h). At day 45, ET plasma levels and ET urinary excretion were as follows:

	ET plasma (pg/ml)	ET urine (pg/24h)
RMR (n=10)	2.00±1.02	86.7±39.6*
S (n=10)	3.29±1.81	30.5±6.6

Values are mean ± SD. *$p<0.01$ vs S.
These results show an exaggerated production of ET in renal cortex from rats with RMR upon stimulation with thrombin, together with an increased ET urinary excretion, and propose a potential role for this peptide in renal disease progression to glomerulosclerosis.

T

THE TREATMENT OF CRESCENTIC GLOMERULONEPHRITIS (CGN)

G B Haycock

Glomerulonephritis (GN) complicated by crescents (concentric cellular proliferation or infiltration in Bowman's space) has a poor prognosis, with a high risk of rapid progression to renal insufficiency. The results of treatment are difficult to assess for several reasons. First, CGN is not a distinct entity: crescents occur in many types of GN, and the nature of the underlying disease influences prognosis and the response to treatment independent of the extent of crescent formation. Second, there is no agreed definition of a crescent, although most writers require 50-60% of the glomerular circumference to be covered by a layer at least two cells thick, and 50-60% of glomeruli to be involved, in order to diagnose CGN. Third, clinical variables not reflected in the histology may affect outcome (e.g. presence of oliguria, duration of disease). Fourth, the rarity of CGN means that no one centre sees enough cases to undertake comparative studies, even in adult renal medicine where CGN is somewhat more common than it is in children. The absence from the literature of prospective, controlled trials is therefore not surprising, and the results of retrospective, anecdotal reports must be pooled and compared with historical controls to obtain the best available interpretation.

Outcome of untreated CGN Patients with CGN of mixed aetiology and crescents affecting >50% of glomeruli have approximately a 90% risk of renal failure [1]. These figures refer to adults and children combined, but available evidence suggests that age has little effect on outcome [2]. Patients with CGN complicating post-streptococcal GN probably do better, and those with polyarteritis, Goodpasture's syndrome and mesangiocapillary GN worse, than the average. Patients oliguric at presentation rarely recover useful function. Within diagnostic groups, the greater the proportion of glomeruli affected by crescents the worse the prognosis.

Available treatments CGN has been treated with steroids in various doses, cytotoxic (immunosuppressive) drugs, anticoagulants, antiplatelet drugs and plasma exchange. Almost every conceivable combination of these has been used, usually in an uncontrolled fashion: it is impossible in most cases to identify which component or components of combination therapy were responsible for any beneficial effect claimed. However, on the basis of pooled results, the effect of treatment with oral steroids and cytotoxic drugs, with or without anticoagulants and antiplatelet drugs, is to improve renal survival from about 10% to about 50% [1,2,3]. A recent study of children with IgA nephropathy and unfavourable histological and clinical predictors of outcome, including crescents, showed stabilization of function and improvement in histological indices of activity up to 7 years after a one year course of prednisone and azathioprine [4].

Intravenous methylprednisolone (IVMP) and plasma exchange (PE) High dose IVMP (10-30 mg/kg/day), used early in the course of the disease, is reported to be effective in about 75% of children with CGN [3,5]. The use of PE has been described in a few children and its effectiveness appears to be about the same as IVMP [3,6]. Whether combining IVMP and PE gives better results than either alone cannot be answered on present evidence, although a few anecdotally described cases are encouraging. PE is usually combined with cyclophosphamide or a similar drug to prevent regeneration of the putative antibodies or immune complexes responsible for the disease.

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U

THE TREATMENT OF IgA NEPHROPATHY IN CHILDREN

P. Niaudet and R. Habib.

Until the recent years, it was generally accepted that IgA nephropathy was a benign disease in children. Several reports on the long term assessment of these patients have shown that some of them may progress to chronic renal failure. The best pronostic indicators for poor prognosis seem to be proteinuria > 1 g/day and crescents in glomeruli on initial biopsy. Therefore, the therapeutic approaches should concentrate on the treatment of the patients at risk of progression to renal failure.

Several therapeutic trials have been reported. Phenytoin which decreases serum levels of IgA was first reported by Clarkson et al (Clin Nephrol 1980, 13 : 215-8) to reduce both serum IgA levels and the frequency of episodes of macroscopic hematuria. However, these authors as well as Egido et al in a controlled trial (Nephron 1984, 38 : 30-9),found that phenytoin failed to alter the course of the disease. Danazol, a agent which increases serum complement levels was used with the assumption that an impaired solubilization of IgA mesangial immune complexes may be involved in the pathogenesis of the disease. Tomino et al (Am J Kidney Dis 1984, 4 : 135-40) reported a beneficial effect on proteinuria in their patients but there has been no other report on this drug.

Eicosopentanoic acid was used in two recent therapeutic trials (Lancet 1984, 1 : 1017-8, Clin Nephrol 1989, 31 : 128-31). One of them suggested that fish oil may stabilize the progression of renal failure compared to the control group whereas the second trial failed to observe any effect of such therapy. Miura et al (Clin Nephrol 1989, 32 : 209-16) have reported that prolonged therapy with urokinase induced marked improvements in proteinuria and serum creatinine. Antiplatelet therapy with dipyridamole has failed to show any benefit in this condition.

Plasma exchanges have been performed in several patients who showed deteriorating renal function. Although there is no controlled study, it seems that plasma exchanges may alter the course of the disease but only if the exchanges are continued (Seminars in Nephrology 1987, 7 : 393-8).

There have been several reports on the use of prednisone in IgA nephropathy. First, most patients with nephrotic syndrome and minimal change on renal biopsy respond to prednisone and may have a relapsing course. These patients rather have steroid responsive nephrosis with coexisting mesangial IgA deposits. Waldo et al (Am J Kidney Dis 1989, 13 : 55-60) reported beneficial effects of prolonged alternate day prednisone therapy in 6 children with risk factors of disease progression based on clinical and histologic findings. Kobayashi et al (Q J Med 1986, 234 : 935-43) reported similar results with long term daily prednisone in patients with persistent proteinuria and moderate to severe histologic changes only if renal function was preserved at initiation of therapy. Andreoli and Bergstein (Pediatr Nephrol 1989, 3 : 248-53) recently reported on 10 children with severe IgA nephropathy treated with prednisone and azathioprine for 1 year. Protein excretion decreased as well as the activity score on renal biopsy. Because of the encouraging results obtained in severe forms of Schönlein Henoch purpura nephritis with methylprednisolone pulses and because of the morphologic similarities between the two diseases, we undertook the same therapeutic protocole in severe forms of primary IgA glomerulonephritis. We treated 8 children in whom initial biopsy had shown more than 50% crescents. With a follow up of 1 to 5 years, proteinuria had decreased in all patients and none had reduction of glomerular filtration rate. Repeat renal biopsies were performed in 6 patients and showed histological improvement in 5 of them.

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V

I.V. Cyclophosphamide for the Treatment of Lupus Nephritis,

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From 1981-1989, 244 patients were dialyzed at Childrens Hospital of Los Angeles (CHLA); 24 deaths occurred (9.8%). Non lupus death rate was 8.4%. 17 lupus patients underwent dialysis; 5 died (29.4%).

To determine if the progression of renal disease could be ameliorated or end stage renal disease avoided, an intravenous (I.V.) cyclophosphamide protocol was adopted in 1984.

From 1984 to 1990, 20 patients, 17 females and 3 males, received treatment. Their ages were: 1 child 0-5 years; 4, 5.1-10 years; 4, 10.1-15 years; 11, 15.1-20 years. Ethnic distribution was: 9 Hispanic, 4 Black, 4 Asian and 2 Caucasian.

Criteria for entry included: 4 or more American Rheumatism Association revised criteria for the classification of SLE; failure to respond to conventional steroid therapy; active urinary sediment and renal biopsy with active lesions.

Criteria for exclusion were: inability to comply; pregnancy; persistent leukopenia despite steroid therapy (2 months); active infection and end stage renal disease or chronic changes on renal biopsy.

The study design included induction with 7 I.V. doses of cyclophosphamide over a 6 month period and a maintenance phase of every 3 months for 30 months. All infusions were given in the hospital with diuresis. Prednisone was titrated according to therapeutic response and neutrophil count.

Cyclophosphamide was given initially at 0.5 mg/M^2 and peripheral WBC_3 were obtained 10-14 days later. If the WBC was 1,000/mm^3, the dose was increased 25% (maximum 1 gm/M^2). If pre-treatment WBC was 4,000 or absolute neutrophil count was 2,500, drug was held.

The paramenters followed included: history and physical examination, creatinine clearance, urinary sediment, 24 hr urinary protein, C_3, anti-double stranded DNA antibodies (immunofluorescent stain using Crithidia lucillae) and serum chemistries. Percutaneous renal biopsies were obtained in non-hypertensive, non uremic, non bleeding patients at the start (N = 16) and end (N = 9) of the study period and were analyzed by the WHO classification as well as for activity and chronicity.

Data obtained before (N = 20), during or when therapy was discontinued (N = 11) or completed (N = 9) are presented below:

	Clin Act	Cr Cl (Range)	Urine Sed	24 hr Ur. Prot (Range)	Serum Alb (Range)	C_3 (Range)	Anti DNA
PRE	20+	86 ± 57 (35-238)	20+	4.8 ± 5.9 (.78-22.7)	2.5 ± .6 (1.4-3.6)	59 ± 27 (21-114)	13+ 6-
POST	1+ 18-	94 ± 36 (44-170)	6+ 7-	1.38 ± 1.7 (.09-5.2)	3.5 ± .7 (2.0-4.4)	92 ± 22 (52-11)	7+ 6-

During the treatment period prednisone was reduced from 0.99 ± 0.42 mg/kg/day (range 0-1.8) to 0.37 ± 0.39 (range 0-1.45).

Significant adverse effects were minimal; no patient became septic. Hemorrhagic cystitis did not occur. No deaths were due to cyclophosphamide.

Of the original 20 patients, 9 completed the protocol; all achieved clinical remission except 1 with arthritis. Of the 11 patients who did not complete the protocol, 4 were non compliant; 1 died following withdrawal of all therapy, 2 developed ESRD and the 4th has altered renal function. The protocol was stopped in 1 patient who became pregnant. 3 patients chose to end the protocol after 9 doses and remain stable. The remaining 3 are in progress.

Summary and conclusions: I.V. cyclophosphamide is an efficacious land safe therapy for children and adolescents with lupus nephritis with impressive steroid sparing properties during a 6 year study period. Marked improvements in urinary protein excretion, serum albumin and complement were achieved. Whether or not the long term outlook for young patients with significant renal involvement can be improved awaits collection of more data and longer followup.

1

EVALUATION OF 70 PATIENTS WITH A FUNCTIONING GRAFT 10 TO 16 YEARS AFTER RENAL TRANSPLANTATION IN CHILDHOOD.

M.F. Gagnadoux, R. Habib, M. Charbit, D. Malheiros, M. Broyer.

Out of 150 renal transplantations performed between Nov. 1972 and Dec. 1979 in our Institution in 141 children and adolescents aged 4 1/2 to 20 years (yrs), 70 (47%) were fuctioning at 10 yrs (67/145 cadaver kidney grafts and 3/4 living donor grafts). The medical and social status of the 70 patients at latest follow-up of the graft (10 to 16 1/2 yrs, $\bar{m}$ = 12 yrs) was analyzed. Patients (pts) were subdivided in 5 groups according to GFR (ml/mn/1,73 m²) and blood pressure (BP) : 1) GFR $\geq$ 80 ml, normal BP : 23 pts (33%) ; 2) GFR 60 to 80 and/or high BP : 24 pts (34%) ; 3) GFR 40 to 60 : 6 pts ; 4) GFR 15 to 40 : 7 pts ; 5) back on dialysis after 10 yrs : 10 pts. Forty one pts underwent a renal biopsy which showed : 1) 63% of normal or subnormal kidneys, 2) a good correlation between the degree of parenchymal damage and the clinical status at latest examination and 3) the presence of a transplant glomerulopathy in 11. The mean adult height was 155,7 ± 10,4 cms in males and 149,8 ± 10 in females. Osteoporosis was found in 88% of pts whose vertebral bone density was measured, and aseptic bone necrosis was present in 34% of pts. HBs antigen was carried by 37% of pts, half of them having persistent cytolysis. Only 1 cancer was observed (bladder cancer in a child treated with Cyclophosphamide). Six deaths occurred between 10 and 13 yrs form septicemia (2), cancer (1), hepatitis B (1), cerebral cystinosis (1) and sudden death (1). The overall patient survival was 87% à 10 yrs and 83% at 14 yrs, and that of cadaver kidneys was 46% at 10 yrs and 39% at 14 yrs. The rehabilitation was rather satisfactory since 40% were working full-time and 23% continued their education.

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2

ACQUIRED CYSTIC KIDNEY DISEASE - A FREQUENT COMPLICATION IN PEDIATRIC PATIENTS BEFORE AND AFTER RENAL TRANSPLANTATION.

U. Querfeld, F. Schneble, R. Waldherr, K.Schärer

Acquired cystic kidney disease (ACKD) has mainly been reported in adults as a complication of long-term hemodialysis treatment. We studied 35 pediatric patients (age 7-26 years) by renal ultrasound (US), 0.6-15 (median 6) years after the onset of ESRD, defined as the start of maintenance dialysis treatment. At the time of investigation, 27 patients (77%) had a functioning renal transplant, and 8 patients were treated by maintenance dialysis (5 HD, 3 CAPD). Cysts were detected by US in 22 patients (63%); of these,10 (29%) had bilateral multiple cysts which were diagnosed as ACKD. Twelve patients (34%) had unilateral solitary or multiple cysts.
A 26 year-old dialysis patient who had undergone dialysis treatment for a total of 15 years had evidence of ACKD and bilateral renal tumors on US; the histology of the nephrectomy specimens disclosed widespread renal carcinoma. No metastases were found. In addition to renal cysts,nine patients (25%) had small echogenic areas on US resembling smaller tumors, e.g. adenomas.
We conclude that acquired renal cysts are present in over 60% of pediatric patients with a history of chronic renal insufficiency including patients with a functioning renal transplant. Because of the known increased risk for the development of renal adenocarcinoma, these patients should be regularly monitored by US, even after successful transplantation.

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3

PROSPECTIVE STUDY OF THE URINE ACIDIFICATION DEFECT IN ACIDOTIC CHILDREN WITH RENAL TRANSPLANT.

M Déchaux, A Caldas, G Guest, K Laborde, M Broyer.

Mechanisms involved in hyperchloremic acidosis frequently observed in children with renal transplant are not clearly described. The aim of this study was then to evaluate1) the renal acidification defect in these patients and 2) the hormonal status presumely implicated in this trouble.
Two groups of children with a renal transplant have been studied : the first one included 13 children with chronic hyperchloremic and normokalemic acidosis and the second group 9 age-matched children (6 to 18 years) with a normal acid-base status (control group). In all these transplanted children immunosuppressive treatment includes prednisone, azathioprine and ciclosporin. Urine Net Acid Excretion (NAE), urine pH, were measured when children were acidotic: plasma bicarbonate less than 18 mmol/l, spontaneously or after NH4Cl load. On the same day plasma hormonal status was evaluated : PTH (1-84 RIA), 25 (OH) D3,1-25 (OH)2 D3, Plasma Renin Activity and plasma Aldosterone. Glomerular filtration rate was measured as classic Inulin Clearance (Cin). Results are reported in the table

	ACIDOTIC CHILDREN		CONTROL GROUP
Urine pH	>6		<5.5
NAE µmol/mn/m2	20.2±10.4	p<0.01	32.3±9.0
T.A µmol/mn/m2	6.6 ± 5.0	p<0.01	12.6 ± 2.9
NH4 µmol/mn/m2	12.1 ± 6.7	n.s	13.3 ± 4
NAE µmol/100ml GFR	65.9 ± 39.5	p<0.05	92 ± 27.1
PTH pg/ml	100.5 ± 70	p<0.01	45.5 ± 29
Renin ngAgI/ml.h	12.2 ± 17.0	p<0.05	4.1 ± 8.2
Aldosterone ng/dl	85.6 ± 55	p<0.01	63 ± 74
ANF pg/ml	85.6 ± 54.5	n.s.	63.6 ± 7
C_{In}ml/min/1.73m2	34.6 ± 11.4	p<0.01	51.3 ± 11.1

In acidotic transplanted children, unlike in acidotic children with chronic renal failure, the ability of the kidney to generate a normal gradient of hydrogen ion and lower urinary pH was impaired. Neither hyporenin hypoaldosteronism nor plasma volume expansion (as measured with plasma ANF concentration) were involved in this acidification defect. A proximal bicarbonate wasting related or not to hyperparathyroidism cannot be excluded from the present data. Determination of the respective role of dietary phosphate load, reduced GFR, chronic rejection and/or ciclosporin nephrotoxicity need further investigation.

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4

RENAL REPLACEMENT THERAPY IN INFANTS AND TODDLERS

J.H.H. Ehrich and G. Rizzoni

Renal replacement therapy (RRT) in young children is a special problem and only a limited number of cases have been published. Therefore, the EDTA Registry studied informations on children who were aged less than 24 months at start of RRT. Data of 217 young children (36% girls, 64% boys) were analysed who were reported to EDTA between 1978 and 1987 from different countries (France 29%, Italy 17%, UK 13%, Benelux 12%, FRG 10%, others 19%). The acceptance rate of young children for RRT has increased in recent years. Main causes of chronic renal failure were hypoplasia and dysplasia followed by HUS, glomerulonephritis and pyelonephritis. The first method of treatment has changed recently and in 1985 - 1987 CAPD was performed in 50% of young children, haemodialysis in 32%, IPD in 12% and transplantation in 6%. The 3 years survival of children aged less than 2 years was 70% and thus less than in the age groups of 2 - 6 (80%) and 7 - 15 (90%). It is concluded that cronic renal failure in infants and toddlers can effectively be treated by renal replacement therapy. However, treatment should be performed in specialised centres because of the risk of complications due to the underlying diseases or to RRT in this young age group.

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5

SUCCESSFUL TREATMENT OF PRIMARY HYPEROXALURIA (PH), TYPE I, BY COMBINED HEPATIC RENAL TRANSPLANTATION (tx).

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PH type I is an autosomal recessive inborn error of metabolism resulting from a deficiency of the hepatic enzyme alanine: glyoxylate aminotransferase (AGT). The results of combined hepatic and renal tx in 3 boys are discussed. Patient 1 presented at 1.5y with urolithiasis, patients 2 and 3 in end stage renal failure at 14 and 6 y respectively. Liver biopsy confirmed AGT deficiency in all patients. All required chronic dialysis at the time of tx; total hepatectomy was performed in all and native kidneys were left in situ.

Patient	Age at tx years	Age at follow up years	G.F.R. ml/min/1.73m²	URINE oxalate mmol/1.73m² SA/24h	URINE glycollate mmol/1.73m² SA/24h
1	10.0	11.6	81	1.00	0.72
2	14.6	15.6	48	1.15	1.04
3	7.7	8.3	113	4.32	2.38

Successful engraftment of both organs was achieved in all patients using triple immunosuppression; cyclosporin A, azathioprine, prednisolone. Post operative dialysis was not required, and liver function has remained normal. However, plasma oxalate levels have remained elevated (>3.0 µmol/l) and both urinary oxalate (>0.46 mmol/1.73m² SA/24 h) and glycollate excretion remained increased reflecting excretion of the persisting systemic oxalate burden especially in bone, or endogenous oxalate production. To date the results of renal tx alone in PH have been poor and regular dialysis cannot keep pace with the excessive rate of oxalate production, combined hepatic renal tx should therefore be considered the treatment of choice in end stage renal failure.

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6

HYPEROXALURIA TYPE 1: SIMULTANEOUS LIVER AND KIDNEY OR ISOLATED LIVER-TRANSPLANTATION ?

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The biochemical basis of primary hyperoxaluria type 1 (PHI) is the lack of liver cell peroxisomal enzyme alanine:glyoxalate aminotransferase which transfers glyoxalate to glycine. Combined liver and kidney transplantation (TPL) is able to correct the metabolic defect and to reverse chronic renal failure (CRF). We report on 2 children with PHI (confirmed by enzyme studies from liver biopsy) of whom the one underwent isolated liver TPL and the other hepatorenal TPL.

Case 1: In 1986, CRF was diagnozed in a female infant. At the age of 2, liver TPL was performed after pyridoxine-resistant PHI had been diagnozed. After TPL, serum oxalate (S-OX) declined from >70 to <10 umol/l within the next 12 months. Urine oxalate (U-OX) normalized rapidly, but an elevated excretion was diagnosed during the third month post TPL (900 mmol/mol creatinine). Nephrocalcinosis did not progress and C_{CR} stayed stable about 12 ml/min/1.73m² for 18 months.

Case 2: In July 1989, a combined liver and kidney TPL from the same donor was performed in a 4 1/2 year old boy while on chronic hemodialysis treatment. P-OX and U-OX normalized within one week. U-OX was low during the next months (<40 mmol/mol cr), but increased up to 100-260 during month 4 and 5 and was again <40 within the following weeks. As in case 1, this was interpreted as oxalate mobilization from body stores. Both transplanted organs continue to have a good function (GOT, GPT,GGT <20 U/ml, C_{CR} 65 ml/min/1.73m² 11 mo. post TPL). Simultaneous hepatic and renal TPL is a new possibility of effective treating children with PHI. If the patient has not reached terminal renal failure, isolated liver TPL may also preserve from progression of CRF.

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7

SUCCESSFUL LONG-TERM OUTCOME OF KIDNEY TRANSPLANTATION (Tx) IN CHILDREN WITH TYPE 1 HYPEROXALURIA (HO)

A. Kátz*, Y. Kim, J. Scheinman, J.S. Najarian & S.M. Mauer

Recently, combined liver-kidney Tx has been advocated as the therapy of choice in patients (pts) with ESRD, due to HO. It seemed timely, therefore, to review the outcome of kidney-only Tx in children with HO.

11 kidney Tx were performed in 8 children age 5mo-7,5y, All presented with nephrocalcinosis, 6 within the first year of life. All pts. had extra-renal oxalate (Ox) deposits,Time on dialysis ranged from 3-13 mo, All but one had living related donor grafts, All underwent combined hemo and peritoneal dialysis one week prior to Tx, In order to maximize GFR, and thereby Ox excretion, CsA was not used, Pts were maintained on high fluid intake, pyridoxine, phosphate, magnesium and thiazide diuretics,

4/8 pts died, 7/11 grafts failed, 5 within 3 mo of Tx, In 5/7 failure was associated with a decrease in GFR due to rejection, obstruction, infection or renal infarction, In 2 the etiology of graft failure remains unclear, 4/8 children have functioning grafts (2 second grafts), Graft follow-up is 3-7.5y. Ccr ranges from 70-110ml/min/1,73m, Graft biopsies show no recurrence although urinary Ox excretion is elevated in all 4. There was no correlation between age at presentation, time on dialysis, urinary Ox excretion and outcome.

Kidney Tx alone proved to be a valid treatment modality in 50% of the patients. Medical reduction of Ox production, increase in its urinary solubility, early Tx and aggressive pre-Tx dialysis improve outcome. The role of the liver Tx is not yet well-defined; success without liver Tx is certainly possible.

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8

THE CHANGING PATTERNS OF END STAGE RENAL FAILURE IN CHILDREN

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There is only one paediatric nephrology unit serving the North Western Regional Health Authority of England. This is a well defined geographical region with a relatively stable population. Thus we are able to describe the changing patterns of end stage renal failure. Between 1968 and 1987 108 children with ESRD had been treated [62 males, 46 females]. There has been a steady increase in the number of patients under 15 years of age at onset of ESRD in successive 5 year periods, with an increasing proportion of males, patients with congenital renal disease and age under 5 years. Renal replacement was initially with haemodialysis and latterly CAPD. 139 transplants [134 cadaver and 5 live donor] were performed 6 of these were pre-dialysis. 20 deaths have occurred, 6 [30%] of which were directly related to the transplant. Early deaths are now very rare. In June 1989, 88 [81%] were alive, 66 [61%] with a functioning graft, 21 [19%] on dialysis. Final adult height achieved was better in females. Preliminary data suggests that growth is worse in patients currently under 18 years old compared with adult survivors. Rehabilitation and adjustment in adult survivors is the subject of a separate report.

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9

PSYCHOSOCIAL ADJUSTMENT OF ADULT SURVIVORS OF A PAEDIATRIC END STAGE RENAL FAILURE PROGRAMME

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Of patients commencing treatment for ESRD in our paediatric unit between 1968 and 1987 50 patients are now over 18 years of age [mean age 25 years range 18-30 years]. 45 of these patients agreed to be interviewed for a study of psychosocial adjustment. The interview was semi-structured and comprised a modified social stress and support inventory, a modified lifetime schedule for affective disorders and schizophrenia, and an enquiry into the subjective experience of illness, treatment, treatment and coping. Subjects completed the parental bonding instrument and Rosenberg's self esteem questionnaire. A significant level of psychiatric problem was identified. 27% had a professional contact for a psychiatric problem before the age of 17 years. This falls to 15.5% since that age but 42% describe psychological disorder reaching criteria for a definite research diagnostic criteria diagnosis from the age of 17 on at least one occasion.

75% of patients were single with 66% living with parents. 48% were in full time employment and though only 16% were registered disabled, 30% were currently living on DHSS benefits alone. 71% felt schooling was markedly affected by illness/treatment. Problems with regards to personal relationships, physical appearance and coping methods were also explored. There are clearly ongoing problems with psychological adjustment in adult life and these seem to be seriously under-recognised. On the other hand some patients with conventional indicators of poor adjustment [unemployed, single, living at home] were shown by the interview to be well adjusted thus conventional criteria for adjustment need to be reviewed. We hope to indentify risk factors which predict for problems in adulthood.

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PLASMA IMMUNOREACTIVE ATRIAL NATRIURETIC FACTOR CONCENTRATION (piANF) : INDICATOR OF CIRCULATING VOLUME STATUS IN HEMODIALYSED (HD) CHILDREN.

K.Laborde, I.Thiriet, MF.Gagnadoux, A.Bensman, C.Sachs, M.Broyer, M.Dechaux.

Indirect evidences suggest that volume overload is the major determinant of piANF elevation in HD patients. The relationship between piANF and extracellular fluid volume (ECV) was investigated by determining both parameters in 30 HD children (aged 1 to 17.5 years; 18M, 12F) 24 hours after dialysis. piANF was determined using a commercial RIA (Amersham) after plasma extraction (Sep-Pack C18); ECV was estimated from inulin distribution volume determination and expressed as %BW. In HD children piANF ranged from 43 to 427 pg/ml (control age-matched children: 30-70 pmoles /ml) and ECV from 17 to 33%BW; a significant positive correlation was observed between piANF and ECV ($r=0.66$; $p<0.001$). Patients who presented hypotension during dialysis had lower piANF (133±90 vs 211±123 pg/ml) and ECV (23±3 vs 26±4%BW) than children who had a good tolerance . On the contrary, patients who needed permanent antihypertensive therapy had higher piANF (204±122 vs149±100 pg/ml) and ECV (26±4 vs 23.5±4.5 %BW) than non-treated patients. In a few children in whom iterative determinations were performed, individual piANF and ECV changes were in close agreement and both parameters were well correlated.
In HD children , volume status is difficult to assess and is of critical importance in the determination of end-dialysis body weight, specially in presence of hypertension; in these situation,as piANF is directly related to ECV it appears as an instantaneous and reliable indicator of volume status; its determination may therefore provide a usefull and easy to perform alternative to classic methods of ECV determination.

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HEPATITIS C (HC) AND DETECTION OF HC VIRUS (HCV) ANTIBODIES IN A PEDIATRIC DIALYSIS UNIT

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The recently identified HCV appears to be a major cause of transfusion-associated and sporadic Non-A-non-B-hepatitis (NANB-H). Its diagnosis depends on the detection of HCV-specific antibodies (AB). Little is known about incidence, morbidity and transmission rates of HCV infections under renal replacement treatment.
Using an enzyme-linked immunoassay (Ortho Diagnostic System) with a recombinant HCV-associated polypeptide (Chiron Corp.) sera from pts on chronic hemo- (HD) and peritoneal dialysis (PD) or after renal transplantation (Tp), and the medical staff were examined for the presence of HCV-AB.
Three of 9 pts predominantly treated with HD, and 1 of 10 staff members, but none of 9 pts with PD were found to have elevated HCV-AB. Pt groups did not differ significantly in respect of duration of dialysis and number of blood transfusions (HCV+ vs HCV-, or HD vs PD; all $p > 0.05$). Retrospective analysis revealed intermittent courses of elevated aminotransferase activities without jaundice in the pts with anti-HC AB while on HD. A nurse with acute Hepatitis C, on the other hand, presented with malaise and icterus, recovering completely. Tp and immunosuppressive therapy were well tolerated in 2 pts with HCV-AB without recognizable recurrences of hepatitis.
In view of the experience with NANB-H the long term prognosis in the subform of dialysis-associated HC is questionable. PD pts seem to be at lower risk to acquire HCV infections. Regular screening for HCV-AB and meticulous adherence to hygienic techniques are undispensible, in order to avoid viral transmission within the dialysis unit.

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THE ROLE OF URINARY ALUMINIUM (U-Al) EXCRETION FOR THE DETECTION OF AL ACCUMULATION IN CHILDREN WITH NON TERMINAL RENAL FAILURE (NTRF).

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In previous investigations we have confirmed the DFO test by means of serum Al (S-Al) determination to be the most reliable indicator of Al overload in anuric children with terminal renal failure. To elucidate its value in children with NTRF we investigated not only the changes of S-Al but also of U-Al after DFO (1 g/m^2) adminsration in 5pts on conservative treatment (CT, mean age 15.6 yrs, Scr 13 mg/dl) and 8 pts after renal transplantation (TP, mean age 15.4 yrs, Scr 1.5 mg/dl). By means of atomic-absorptionspectrophotometry S-Al was measured before, 3, 17, 24, 44, and 48 hrs after DFO and U-Al by collecting the urine over a period of 9 hrs before and 15, 24 and 9 hrs after DFO. Data were correlated with the calculated cumulative oral Al load (0-630 g/m^2). The median basal S-Al, maximal S-Al and maximal increase of S-Al (Δmax) were 47.2, 62.5 and -12.8 μg/l respectively in CT and 17.0, 56.3 and 21.7 μg/l respectively in TP. U-AL in both groups was 15.4 μg/12 hrs before DFO and 22.1 μg /12 hrs after 15 hrs and 93.1 μg/12 hrs after 39 and 124 μg /12 hrs after 48 hrs of DFO administration. The maximal median U-Al was 44.4, the Δmax U-AL 42.8 μg/12 hrs. Whereas none of the S-Al values correlated with the cumulative oral Al load there was a significant ($p < 0.03$) correlation of this parameter with all the U-Al values measured: $r > 0.60$. The strongest correlation was calculated between the cumulative oral Al load and U-Al excretion over 15 hrs after DFO ($r = 0.79$, $p < 0.001$). Data demostrate that in pts with NTRF U-Al is more indicative of the amount of Al accumulated rather than S-Al is, which must be taken into consideration when performing a DFO test. (DFO = deferoxamine)

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THE EFFECT OF ERYTHROPOIETIN ON THE CELLULAR DEFENCE MECHANISM OF RED BLOOD CELLS IN CRF PATIENTS

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The changes of glutathion (GSH), redox ratio (GSSG/GSH) and hemoglobin (Hb) oxydation, the activity of antioxidant enzymes: superoxide dysmutase (SOD), catalase, glutathion peroxidase, as well as the concentration of lipid peroxidation (LPO) product (malonyl-dialdehyde MDA) in the red blood cells (rbc) were studied during Erythropoietin (EPO) treatment given i.v. 3x50 mg/week in 9 patients with chronic hemodialysis. The stability of GSH and Hb was tested by an in vitro oxidative stress (acetylphenylhidrazine (APH)). After a 2-3 weeks of EPO treatment a rapid and transient elevation was observed in the level of Hb and Htc, accompanied by a consecutive increase in GSH (from 7.38±1.32 to 13.81±1.39 μM/g Hb). This was followed by a marked increase of GSSG concentration (from 17.6±3.6 to 947.7±261 nM/g Hb). In the first 4-6 weeks period of treatment GSSG/GSH became very high. The stability of GSH decreased in APH test (from 0.76±0.19 to 0.25±0.09 %).The concentration of Hb oxidation products (metHb, COHb) increased indicating a hemolytic process.Following the 7th week both GSH and GSSG concentration returned to the initial values, the stability of GSH improved, the level of oxidation products of Hb reduced.LPO changed simultaneously, after a transient elevation MDA decreased ($p < 0.01$). Amongst the antioxidant enzymes SOD exhibited a significant decrease (from 512.2±229.5 to 140.0± 85.2 U/g Hb $p < 0.001$).These results relate to a significant activation in GSH metabolism with an increased turnover of Hb in the early period of EPO therapy. This may contribute to an increased sensitivity of rbc-s to the oxidative injury of CRF patients.

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MECHANISMS OF ANOREXIA AND VOMITING IN CHILDREN WITH CHRONIC RENAL FAILURE.

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Feeding difficulties are common in children with chronic renal failure (CRF) but there has been little investigation into the underlying pathophysiology. We studied oesophageal and gastroduodenal motor function in 12 symptomatic children with CRF. 10 children without renal disease undergoing the same investigations with normal results acted as controls. 6 hour post-prandial intra-oesphageal pH monitoring was used to detect gastrooesophageal reflux (GOR). Gastric half-emptying time (T/2) of a 5% glucose and/or a milk meal was assessed by applied potential tomography (APT). Gastroduodenal electrical control activity (ECA) was recorded by surface electrogastrography (EGG) and subjected to spectral analysis to determine the dominant frequency present. Candidate humoral factors were measured by radioimmunoassay of fasting glucagon, gastrin, neurotensin, vasoactive intestinal polypeptide and pancreatic polypeptide. 7/12 patients had significant acid GOR (reflux index 7-22% in CRF, 1%-5% in controls), 7/12 had an abnormal gastric T/2 (2 CRF 25', 18' controls 7'-15' after glucose; 5 CRF , controls 26', 27' 82', 90', 100, controls 36'-72' after a milk meal). 6/11 had abnormal ECA with gastric dysrythmias at 1-1.5 and 6-7.5 cpm (normal frequency 3 cpm). In 8/10 fasting gastrin was elevated (53-400 pmol/l, controls <40 pmol/l) but no other consistent humoral abnormality was found. All the children with anorexia, vomiting and CRF had one or more disorders of foregut motility. These findings and the elevated levels of serum gastrin suggest that an altered humoral environment generated by CRF is responsible for the disordered foregut motility and resulting symptoms.

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LHRH PULSATILE SHORT-TERM ADMINISTRATION IN UREMIC CHILDREN WITH DELAYED PUBERTY

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Pubertal development is frequently delayed or disordered in children with CRF.The mechanisms of the abnormalities of pituitary-gonadal axis in uremia are still unclear.Pulsatile nocturnal variations of LH have not been found in children with ESRF,phenomenon which could be linked to a damage of the hypothalamic LH discharge.On this basis we tested the short-term effects of exogenous LHRH administered in a pulsatile way in 3 boys,14-15.5 years old,with long-lasting CRF and delayed puberty (P1-P2).Bioactive(b) LH,immunoreactive(i) LH,iFSH,testosterone(T) and 17-OH-Progesterone(P) have been evaluated before and during 7 days of s.c. LHRH (150 ng/kg BW every 120 min) administered with a wearable pump.On days 0 and 7 blood was collected every 15 min for 4 hours;on days 1,3 and 5 once 60 min after drug delivery. iLH,FSH,T and P were measured by RIA,bLH by RICT according to Dufau method with minor modifications.
In basal conditions there was no pulsatility of LH and b/i LH ratio was reduced.Exogenous LHRH induced in all subjects an increase in bLH,iLH,FSH,T and P.The b/i LH ratio was increased and this phenomenon appeared more pronounced in the P2 child. These preliminary data suggest a key role of the central (hypothalamic? suprahypothalamic?) impairment of gonadostat which is responsible of the disturbances of pubertal development in uremic children.The potential role of pulsatile LHRH therapy in reducing the distress syndrome linked to delayed puberty,needs at present confirmation.

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AMBULATORY BLOOD PRESSURE MONITORING (ABPM) FOR THE EVALUATION OF BORDERLINE HYPERTENSION.

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We evaluated the reliability of ABPM in children, and its diagnostic value in borderline hypertension (HT).
We used the Nippon Colin (NC) ABPM 630 recorder, which measures BP by auscultatory and oscillometric technique simultaneously. In 61 children, age 12±3 yrs, the percentage of measurements that failed was 14% (470/3399) by oscillometry, 26,5% (893/3360) by auscultation, 2,7% (150/5546) after reciprocal supply of both techniques. Comparison of NC auscultatory and simultaneous Hg manometer readings (n=50) indicated slightly lower diastolic BPs with NC device (-3.8±4.9mmHg,$p<0.01$). Comparison of the NC 2 methods (n=1580) showed that systolic readings were slightly more elevated (+2.5±4mmHg,$p<0.001$) and diastolic readings slightly lower (-5±4,$p<0,001$) by oscillometry.
ABPM was performed on 34 occasions in 28 children, mean age 13.3 yrs (8 to 17), suspected of borderline HT from office BP measurements. The number of ABP readings was 44±5 during the day, 9±1 during night. The mean values of ABPs during the day were analysed with reference to the normal resting BP values established in France. This led to reclassify the 34 cases as follows : Group (Gr) 1 : normal ABP (<97th perc), n=18. Gr 2 : borderline ABP (>97th perc, <97th perc + 10 mmHg), n=10. Gr 3 : established AHT (>97th perc + 10 mmHg), n=6.
The percentage of systolic and diastolic ABPs over the 97th perc was : 1) day time, Gr 1 : 18±4 and 26±10%, Gr 2 : 46±19 and 64±16%, Gr 3 : 77±18 and 87±13%. 2) night : 7±10 and 6±11%, 15±10 and 14±13%, 45±28 and 73±24% in Gr 1,2 and 3 respectively.
In conclusion, ABPM appears to be a valuable tool for the evaluation of borderline hypertensive children, allowing a more accurate approach of the true BP load of each subject.

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Increased renal tubular Na-K ATPase activity in Milan hypertensive rats in the prehypertensive period.

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Milan hypertensive rats (MHS) develop hypertension around the third-fourth week of life and exhibit an increased activity of sodium pump in adulthood.
The present study was performed to evaluate whether or not increased Na-K ATPase activity develops before hypertension. Total and ouabain sensitive ATPase activities were studied in single microdissected mTAL (medullary thick ascending limb of Henle) tubules from Milano hypertensive (MHS), Milano normotensive (MNS) and Sprague-Dawley (SD) rats at 22-24, 26-28 and >45 days postnatal age.
The data are given as mean±SE. ATPase activity is given as pmol Pi/mm tub/h; arterial blood pressure as mmHg.
At 22-24 days no difference was seen between MHS and MNS. At 26-28 days MHS had a higher total and Na-K ATPase activity than MNS (3031±171 vs 2471±178, $p<0.05$, n=10; 2289±205 vs 1653±151, $p<0.05$, n=10). At this age there was yet no difference between mean arterial blood pressure (98±5 vs 90±7). Adult MHS had higher blood pressure (140±9 vs 112±8, $p<0.001$) and higher total (3584±136 vs 2718±215, $p<0.01$, n=10) and Na-K ATPase (2670±99 vs 1942±217, $p<0.05$, n=10) than adult MNS.
We conclude that an increased ATPase activity in mTAL precedes the development of hypertension in the Milano strain of rats.

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RENAL ARTERY DISEASES IN CHILDREN.G.Deschênes, M. Zitek, M.Broyer,M.C. Gubler.

Between September 1955 and January 1990, 94 patients (pts) with renovascular hypertension secondary to renal artery occlusive disease were observed. Fifty boys and 44 girls aged from 4 days to 17 years (median = 7 years) presented with hypertensive encephalopathy or myocardiopathy (34 pts), mild or moderate symptoms of hypertension (36 pts) or were asymptomatic (24 pts).
Sixty five patients were classified according to clinical, radiological and histological features : neurofibromatosis (17 pts), fibromuscular dysplasia (11 pts), diffuse arterial calcified elastopathy (11 pts), renal artery thrombosis (10 pts), Williams syndrome (4 pts), Takayasu disease (3 pts) and miscellaneous (9 pts). The classification of the remaining 29 patients was based exclusively on radiological features : unilateral renal artery stenosis (15 pts), bilateral renal artery stenosis with or without associated aortic stenosis (11 pts), miscellaneous (3 pts).
Surgical treatment consisted of 47 renal revascularisations (14 aortorenal bypass, 8 aortorenal reimplantations, 9 anastomosis in the upper mesenteric arterial system, 7 autotransplantations, 4 resections and reanastomosis and 5 miscellaneous). Fifteen renal revascularisations (32%) failed (14 thrombosis, 1 disunion); residual or relapsing stenosis occured in 12 , and 25 (53%) had a good anatomic result. Hypertension was cured in 16/40 patients (40%).Twenty one primary nephrectomy (Nx), 4 partial Nx and 9 secondary Nx led to the normalization of the blood pressure in 25 patients
Twenty percutaneous renal angioplasties (PRA) were performed on 14 patients. Eight were unsuccessful, 4 left a residual stenosis, and 8 had a good anatomic result. Thrombosis did not occur after PRA and hypertension was cured in 7/14 patients.
In conclusion ,1) The main causes of renovascular hypertension in children are fibromuscular dysplasia, neurofibromatosis and diffuse arterial calcified elastopathy,2) Percutaneous renal angioplasty seems to be safer than surgical renal revascularisation and should be considered as the primary treatment of renal artery stenosis in children.

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DIFFUSE ARTERIAL CALCIFIED ELASTOPATHY (DACE) WITH RENOVASCULAR HYPERTENSION (HTA) AS THE FIRST SYMPTOM OF PSEUDOXANTHOMA ELASTICUM (PXE) IN CHILDREN.

M.C. Gubler, G. Deschênes, M. Zitek and M. Broyer.

Vascular involvement and HTA are known to occur in one dominant and one recessive forms of PXE. However PXE is rarely reported as a cause of renovascular HTA in pediatric series.

Among 94 children investigated for renovascular HTA in our institution, 11 have been recognized as having PXE. They were 6 boys and 5 girls, 2 to 12 years old at onset of clinical symptoms related to hypertension. Eight of them originated from North Africa and 3 were born from consanguineous parents. Hypertension was severe, persistent, renin-dependent and associated with arterial bruits and/or asymetry of peripheral pulses in 3 patients.Intravenous urography showed renal asymetry in 3 patients. Renal arteriography was normal in 3 patients and demonstrated irregular stenosis of renal arteries and/or their branchs in 7, associated with extrarenal arterial involvement in 4 of them.
Diagnosis of DACE was based on 1) the finding of increased echoes of interlobar and/or arcuate arteries on renal sonograms (6/8) and 2) the presence of extensive calcifications of the elastic membranes of renal arteries (1/1), intrarenal arteries on renal biopsy specimens (6/6) and superficial temporal arteries (8/8).
Etiologic investigations remained negative in 4 patients (3 to 10 years old at last investigation). Family history of autosomal dominant PXE was present in 1 patient. Angioid streaks on funduscopic examination, severe myopia and/or typical PXE located in the skin of the neck, were detected in 6 patients (9 to 16 years old at last investigation) either at presentation or during the follow-up period.

In conclusion: DACE is an underdiagnosed cause of HTA in children. In our series it accounts for about 12 % of renovascular HTA. HTA with DACE may be the first clinical symptom of PXE.

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BARTTER-LIKE SYNDROME, HYPOMAGNESEMIA ASSOCIATED WITH HYPOCALCIURIA, AND ISOLATED HYPOCALCIURIA: LATE RENAL SEQUELAE AFTER TREATMENT WITH CISPLATIN

M.G. Bianchetti, C. Kanaka and O.H. Oetliker

Frequency and extent of persisting renotubular dysfunctions after cisplatin have not been assessed in children and adolescents.
Ten patients aged from 4 to 20 years had been treated with combined chemotherapy including cisplatin (global dosage ranging from 310 to 1710 mg/m²) and were relapse free and healthy 4 to 43 months after stopping treatment. Mean plasma creatinine (and the glomerular filtration rate calculated using the "creatinine-height formulas"), urea, albumin, sodium, chloride, phosphate, urate or calcium, and the urinary excretion of sodium, chloride, potassium, magnesium, phosphate, urate, protein or glucose were comparable in patients and controls. The osmolality in the first morning urine was >600 mmol/kg in all patients. Mean calciuria ($P<.01$), magnesemia ($P<.01$) and potassemia ($P<.05$) were reduced and bicarbonatemia ($P<.05$) increased in the group of patients when compared with a control group. A more extensive analysis of calciuria, magnesemia, potassemia and bicarbonatemia revealed the following: calciuria, magnesemia, potassemia and bicarbonatemia were normal in 2 patients, calciuria was below the -2 SD control range in 8 patients, renal magnesium wasting was demonstrated in 4 patients (all of them being hypocalciuric as well), and a tendency towards hypokalemic metabolic alcalosis was present in 3 patients (all with hypomagnesemia and hypocalciuria as well). The tubulopathy post cisplatin was therefore ranked as absent (2 patients), mild (isolated hypocalciuria; 4 patients), moderate (hypocalciuria and renal magnesium wasting; 1 patient) or severe (hypocalciuria, hypomagnesemia, and hypokalemic metabolic alcalosis; 3 patients). The cumulative dosage of cisplatin correlated inversely ($P<.05$) with the corresponding calciuria or magnesemia.
Conclusions: 1. Persisting renotubular dysfunctions occur in about three quarters of the patients treated with cisplatin. 2. Contrary to common notion, hypocalciuria occurs more frequently than renal magnesium wasting. Both hypocalciuria and hypomagnesemia are directly related to the global dosage of cisplatin. 3. The severe form of persisting cisplatin tubulopathy includes hypocalciuria, hypomagnesemia and mild hypokalemic metabolic alcalosis and remembers some features of Bartter's syndrome.

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NH_4Cl METABOLIC ACIDOSIS AND THE ACTIVITY OF RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM IN CHILDREN

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The present study was undertaken to assess the effects of acute metabolic acidosis on the activity of renin-angiotensin-aldosterone system in 12 children with a mean age of 8.9 years who underwent NH_4Cl loading test.

NH_4Cl was given in a dose of 0.15 g/kg/day for 3 consecutive days to evaluate renal acidification. Prior to and following NH_4Cl administration blood acid-base parameters,plasma and urinary electrolyte,creatinine and aldosterone (Aldo) concentrations as well as plasma renin activity (PRA),urine flow rate and net H^+ excretion were measured. PRA and Aldo concentration was determined by using RIA methods.

NH_4Cl administration significantly depressed blood pH ($p < 0.05$),bicarbonate ($p < 0.01$) and base deficit ($p < 0.01$) and resulted in a slight, but significant elevation of plasma potassium and chloride concentration ($p < 0.05$).Furthermore,NH_4Cl ingestion induced a marked increase in urine flow rate ($p < 0.01$) and urinary sodium excretion ($p < 0.01$).In response to NH_4Cl metabolic acidosis PRA doubled (4.72±1.18 vs 8.13±1.02 ng/ml/h, $p < 0.05$) and there was a nearly fourfold increase in plasma Aldo level (0.49±0.12 vs 1.52±0.24 ng/ml, $p < 0.01$) and in urinary Aldo ex retion (19.21±4.30 vs 71.8±13.8 ug/day, $p < 0.01$) The elevated Aldo production observed in this study is assumed to be mediated by the combined effect of sodium and water diuresis-related increased PRA,hyperkalaemia and the direct stimulation of adrenal steroidogenesis by metabolic acidosis.

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CHANGES IN RENAL HEMODYNAMICS AND FUNCTION INDUCED BY INTERLEUKIN-1 IN RABBITS

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The polypeptide Interleukin-1 (IL-1) mediates several hematologic and metabolic changes associated with host response to infection. Recent experimental evidence suggests that it could also mediate the hypotension and the increased urinary flow rate and sodium excretion observed in infectious states. The systemic and renal effects of a bolus intravenous injection of human recombinant IL-1-beta were studied in anesthetized and mechanically-ventilated young rabbits, administered 0.5 (n=9) and 5 (n=8) µg/kg b.w. of IL-1. Untreated control rabbits receiving the vehicle alone (n=9) showed no changes in hemodynamics and renal function troughout the 3-h experimental period. A rapid decrease in systemic blood pressure occurred in IL-1 treated rabbits, from 99.2±3.4 to 82.9±3.5 mmHg (0.5 µg/kg) and from 99.3±4.1 to 69.5+4.8 mmHg (5 µg/kg). Mean blood pressure reached its lowest level after 60 min and remained significantly low thereafter. Rectal temperature increased +1.85°C (0.5 µg/kg) and +0.85°C (5 µg/kg) at the end of the experimental period. Diuresis increased +41.9% (0.5 µg/kg) and +38.8% (5 µg/kg). Fractional sodium excretion (FENa) increased +79.6% (0.5 µg/kg) and +42.7% (5 µg/kg). FECl and FEK also rose. Inulin clearance fell -17.7% (0.5 µg/kg) and -34% (5 µg/kg). Renal blood flow, as measured by PAH clearance, increased +16.4% (0.5 µg/kg) and +18.1% (5 µg/kg), along with increased diuresis and sodium excretion. Filtration fraction rose and renal vascular resistance fell signifcantly. These results demonstrate that IL-1 induces hemodynamic changes similar to those observed in septic shock, associated with increases in renal blood flow, urine flow rate and sodium excretion, features also often observed during infection. The IL-1-induced diuresis and natriuresis, despite severe systemic hypotension and decrease in glomerular filtration rate, is probably related to specific renal properties of IL-1.

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NORMOKALAEMIC PSEUDOHYPOALDOSTERONISM IS PRESENT IN CHILDREN WITH ACUTE PYELONEPHRITIS (AP)

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Hyperkalaemic pseudohypoaldosteronism has been observed in infants with obstructive uropathy and UTI. The present study was designed to determine whether a similar syndrome was also present in children with AP, with or without vesicoureteral reflux (VUR). We studied 32 children (8 M,24 F), aged 6.5 ± 3.1 years, with a diagnosis of AP established by the presence of high fever and flank pain/tenderness. Urine culture grew E. Coli in all cases. Grade I-II VUR was demonstrated in 6 cases, and grade III or higher in 4 cases. Study was performed at diagnosis (period 1), after 3 days on i.v. gentamycin (period 2) and after 21 days of antibiotic therapy (period 3). Findings in blood and in 24 hr urine were compared to those present in 31 normal children (17 M,14 F), aged 8.0 ± 4.4 years (P = NS). Children with AP had no evidence of hyponatraemia or renal Na loss. Despite normal plasma K, renal K excretion was significantly decreased in periods 1 and 2 (TTKG 4.4-4.0 vs 6.6, $p < 0.001$; EF_K 7.5-6.6 vs 12.4 %, $p < 0.001$), coexisting with a significant increase in urine volume and plasma creatinine and a significant decrease in urine osmolallity. All values were normalized in period 3. TTKG did not correlate significantly with blood levels of gentamycin or C-reactive protein. Plasma renin activity was significantly increased in all 3 periods (9.2-7.4-5.0 vs 2.1 ng/ml/hr, $p < 0.01$), and plasma aldosterone was significantly increased in periods 1 and 2 (32.5-37.4 vs 22.5 ng/dl, $p < 0.01$). In normal children a positive correlation existed between TTKG and plasma aldosterone ($r = 0.36$, $p < 0.05$), but this correlation was not present in any of the 3 periods studied in children with AP. The present study demonstrates that children with AP present a renal tubular unresponsiveness to aldosterone which is only manifested by decreased indices of K excretion, without associated hyperkalaemia or renal Na loss. This functional alteration may be directly caused by parenchymal inflammation or be mediated by some E. Coli endotoxin.

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RENAL FUNCTION AND SEQUENTIAL RENOGRAPHY IN BROWN-NORWAY RATS WITH CONGENITAL HYDRONEPHROSIS.

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The long-term functional outcome of congenital hydronephrosis (HN) was studied in male BN rats showing this abnormality in high frequency. We used 99mTc-DTPA Furosemide-renography to assess the presence and degree of 'obstruction', and the contribution of each kidney to the total glomerular filtration rate (GFR). We derived an obstruction score (OS) ranging from 0 to 10, using the time to peak, the 99mTc-DTPA accumulation at 15 min, and the Furosemide-response. Total GFR was measured as the plasma clearance of 51Cr-EDTA. The first measurements were done at the age of 3 months and repeated at the age of 6 and 10 months.

Two groups of 7 and 8 rats with unilateral HN (BN-HN-1 and BN-HN-2) were compared with 5 rats with two normal kidneys. The hydronephrotic kidney (HK) of BN-HN-1 rats showed a high OS at the first renography only. The OS of BN-HN-2 rats remained high.

	BN-Control (n=5)				BN-HN-1 (n=7)				BN-HN-2 (n=8)			
	OS			GFR/	OS			GFR/	OS			GFR/
AGE	LK	RK	%T	100g	CK	HK	%T	100g	CK	HK	%T	100g
3	2.8	2.2	51	0.45	3.9	8.7	50	0.49	2.1	8.4	50	0.45
6	0.0	0.6	50	0.43	0.4	4.4	51	0.42	1.1	7.6	50	0.43
10	1.6	2.8	52	0.44	1.1	4.7	52	0.46	1.1	8.8	50	0.44

LK=left, RK=right, CK=control, HK=hydronephrotic kidney
%T=relative contribution to the total GFR.

During 10 months of follow-up, the presence of a HK did not affect the total GFR. The contribution to the total GFR remained at about 50%, similar to that of intact kidneys in controls. Judged from the Furosemide-renography curve ureteral obstruction is present in BN rats. As GFR remained stable there was no obstruction on the basis of renal functional criteria.

In rats with unilateral HN, the HK is able to maintain a normal GFR during a major part of the normal life-span.

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PRENATALLY RECOGNIZED REFLUX. MEDICAL TREATMENT AND FOLLOW-UP EVALUATION.

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During the last few years the systematic fetal screening by means of ultrasound has led to the recognition of vesicoureteric reflux in the neonatal period before an episode of urinary tract infection.
Thirty-two neonates (25 boys and 7 girls) with prenatally detected pelvic dilation were investigated with cystourethrograms and found to have reflux and prospectively studied during a follow-up period of 2 to 5 years.
Urine culture testing was done at birth and chemoprophylaxis was administrated. Reflux was bilateral in 23 patients; unilateral in 9 patients. None of the neonates had associated other abnormality within the urinary tract; 2 patients had a contralateral multicystic kidney.
Separate glomerular filtration rate using ^{99m}Tc-DTPA was evaluated at 1 - 6 months and once a year.
Six male and 1 female infants were treated surgically at 2 months and 6 months (infection - failure to thrive). Spontaneous cessation of gross reflux occured in 30% of the infants. One could observe a progressive increase of the renal function related to the normal renal maturation and a stabilization in the normal range after 1 year of age in 21 patients. In 3 patients the critical SGFR < 10 ml remained at the same rate. In 8 patients a prononced asymetrical left and right function was observed at 1 month with a relative increase of the function never reaching the normal range.
Our study suggests that reflux identified in asymptomatic neonates is more commonly in newborn boys and is more likely to resolve if the urine remains free of infection. SGFR generally remained normal and increased progressively owing to the normal renal maturation.

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RADIOLOGICAL FINDINGS IN ADULTS PRESENTING IN CHILDHOOD WITH UTI AND VUR.

J M Smellie, P J Shaw, N P Prescod and A R Gillams.

The effect of VUR and UTI on the child's kidney may be the development of scars or impairment of renal growth.

The renal status in terms of renal size and growth was reviewed in 99 patients aged 18-39 (M 15, F 84) who had been treated for UTI and VUR in UCH in childhood and followed until VUR ceased or until late adolescence. 55 had unscarred kidneys and in 44 there was renal scarring, bilateral in 11. Reflux which had extended up to the kidney initially in 83 had ceased spontaneously in 59 and had been corrected surgically in 11.

A limited IVU carried out in 1988/89 was compared with the last urogram performed before the age of 14. No new scars developed but one girl developed a large simple cyst in a previously normal kidney. Among the 55 patients with unscarred kidneys renal growth was within or above 2 SDs of the mean in all but 1.

In the 44 patients with renal scarring the appearance of the scars varied depending on their site and further growth of adjacent normal tissue. Normal areas of parenchyma had continued to grow and this was assessed by planimetry. DMSA scans were also carried out in 41 patients. In the 33 patients with unilateral scarring, there was good contralateral growth. The mean SDS score for the unscarred kidney was +0.8 in childhood and +1.8 in the adults.

In patients with VUR and UTI carefully managed and followed up, no deterioration in any imaging parameter was noted when the kidneys were unscarred. Renal growth was least good in those who presented with extensive scarring and severe VUR.

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THE ABUNDANCE OF NaKATPASE mRNA IS REGULATED BY GLUCOCORTICOID HORMONES IN THE INFANT RAT KIDNEY.

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There is a postnatal increase in NaKATPase in the rat kidney. The most rapid increase in enzyme activity occurs between 10 and 20 days of age and coincides with an upsurge of serum glucocorticoids (GC) level. In 10-day-old rats administration of GC will prematurely increase renal NaKATPase activity as well as tubular reabsorptive and urinary concentrating capacity.
We found that the upsurge in serum GC concentration was also accompanied by an increase in NaKATPase mRNA. This prompted us to further examine the effect of GC on the abundance of NaKATPase mRNA in the developing rat kidney. In this study 10-day-old rats were treated with a single i.p. dose of the synthetic highly specific GC analogue betametasone (T) or with the diluent (C). The renal cortex was removed after 20 min, 1 h and 6 h and the abundances of the catalytic α1, α2 and the regulatory β subunits were determined with Northern blot analysis and quantified with scanning densitometry. After 20 min, the abundances of α1 and β mRNAs were 1.8-2 fold higher in T than in C rats. After 1 h, both subunits were approximately 3-fold increased compared to C rats ($p<0.01$). After 6 h, the α1 and the β mRNAs were 6-7 fold increased in T rats ($p<0.01$). For any sample there was a coordinate change in α1 and β mRNAs relative to control. The α2 mRNA was not present at any time. We also studied the kinetics of the enzyme after purification. In C rats the Vmax for the enzyme was significantly lower than in T rats (329.8 ± 31 vs 630.0 ± 11.5 μmol Pi/mg prot/h). The tissue yield increased from 0.238 in C rats to 0.379 mg/g tissue in T rats. The ouabain affinity was the same before and after GC ($K_{0.5}$ = 123 ± 9 vs 140 ± 14 μM, respectively).
Conclusion: the rapid onset of the GC effect on mRNA abundance suggests that the hormone directly activates both genes for α1 and ß subunits in the developing kidney. GC does not induce the expression of any alternative catalytic subunit. The GC inductive effect might be of importance for the postnatal maturation of the kidney.

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PATHOMECHANISM OF HYPERCALCIURIA IN CHILDREN WITH HYPERPROSTAGLANDIN E_2-SYNDROME (HPES)

Gundy Timmermanns[1], B. Roth[2], and H.W. Seyberth[1]

Previously we have described a hyperprostaglandinuric, hypokalemic tubular syndrome which is different from Bartter syndrome with prenatal manifestation (polyhydramnios), hypercalciuria, and nephrocalcinosis (J. Pediatr. 107: 694, 1985). As PGE_2 appears to play a major pathogenetic role in this disease, we coined the term HPES. Despite the benefits of indomethacin treatment, urinary excretion of Ca^{++} remains elevated in most patients (8/10). For possible additional therapeutic interventions we tried to evaluate the mechanism of hypercalciuria by an oral calcium loading-test (Santos et al., J. Pediatr. 110: 238, 1987), including the determination of plasma levels of intact PTH (normal: 2.4-4.8 pmol/l), and calcitriol (65-150 ng/ml) with and without (5 days) indomethacin treatment (2.8, 1.7-3.5 mg/kg/d; median and range). The results are as following:

	with indomethacin	without indomethacin
urinary PGE_2 (ng/h/1.73 m^2)	5.7 (1.3-32.4)	66 * (21.7-111.4)
PRA (ng/ml/h)	4.4 (1.9-16.3)	49.7 * (16-104)

	calcium loading test			
	pre	post +	pre	post +
Ca^{++}/Cr	0.30 (0.08-0.53)	0.48 (0.21-0.96)	0.25 (0.11-0.84)	0.57 (0.21-1.47)
PTH (pmol/l)	10.5 (5.4-12)	6.9 (3-14)	6.5 * (2.3-9.8)	4.7 * (2.1-8.6)
Calcitriol (pg/ml)	162 (108-236)	168 (110-228)	107 * (64-213)	122 * (74-193)

* $p < 0.05$ (between treatment with and without indomethacin)
+ $p < 0.05$ (between pre- and postloading of Ca^{++})

As fastening urinary Ca^{++} levels are high in most patients (normal Ca^{++}/Cr <0.2) irrespective of indomethacin treatment and as high PTH levels fall during Ca^{++}-loading, we conclude that hypercalciuria in HPES is caused by an almost PGE_2-independent mechanism of renal Ca^{++}-wasting which is associated with secondary HPT.

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GROWTH IN PREPUBERTAL CHILDREN WITH BARTTER'S SYNDROME(BS): EFFECTS OF INDOMETHACIN (I).

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Growth was evaluated retrospectively as standard deviation score for height(HSDS) and growth velocity standard deviation score(GVSDS) in 8 prepubertal children(age at start of treatment < 5 years,mean 1.9±1.9) with BS treated with I(2-5 mg/kg/day,mean 2.8±1.1)and oral K^+(3.5±1.4 mEq/kg/day)for 1 year;2 patients also received spironolactone and 1 mg supplementation. Diagnosis of BS was based on the presence of hypokalemia(K_p< 3.0 mEq/l),with high FeK(42±24%),hyperreninemia(PRA=68±67 ng/ml/h),decreased urine concentration after DDAVP(Osm_u=463±201 mmol/kg)and normal blood pressure.

Results.	HSDS	K_p(mEq/l)	Na_p(mEq/l)	Cl(mEq/l)
basal	-3.6±1.2*	2.4±0.6°	131±5*	90±7^
at 1 year	-0.9±0.9*	3.7±0.7°	142±4*	99±4^

p :< ^ 0.02 ; ° < 0.01 ; * < 0.001

The GVSDS was positive in all children (mean +3.4±2.9). No correlation was found between the GVSDS increase in each patient and the rise in K_p,Na_p,Cl_p. Sporadic gastric pains were observed in 2 patients taking I > 3.0 mg/kg/day,which disappeared in 1 patient after reducing I from 5 to 2 mg/kg day. GFR measured as creatinine clearance was normal in all patients.

In conclusion,I was very active in improving growth in our prepubertal children with BS during the first year of treatment. No side effect was noted other than gastric pains.

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BICARBONATE TRANSPORT IN THE LOOP OF HENLE. THE EFFECTS OF DIFFERENT ACID-BASE AND HORMONAL STATES.

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Recently we have shown that the loop of Henle contribute significantly to urinary acidification. To assess further bicarbonate handling by the loop we investigated loop bicarbonate transport ($JHCO_3$)in several pathophysiological conditions. Rat superficial loops were perfused in vivo from late proximal to early distal tubule. Perfusate was an end-proximal Ringer solution containing ^{14}C-inulin and 15 mM bicarbonate. Bicarbonate concentration in collected fluid was measured by microcalorimetry. Loop $JHCO_3$ was measured during 1)acid-base and 2)adrenal steroid manipulations. In the first set of experiments it was found that $JHCO_3$ was: a) stimulated by acute and chronic metabolic acidosis; b) inhibited by acute metabolic alkalosis and during the recovery phase from chronic metabolic acidosis; c) unaffected by chronic metabolic alkalosis induced by a low potassium diet. In the second set of experiments the role of adrenal hormones was tested. Adrenalectomized rats (Adx) showed a sharp decrease in $JHCO_3$. This was partially restored by physiological replacement of dexamethasone (Dex) and fully restored by the replacement of physiological doses of both Dex and aldosterone (Aldo). Aldo alone increased $JHCO_3$ in Adx rats only when it was given at pharmacological doses. These data demonstrate that the loop of Henle plays a crucial role in modulating bicarbonate reabsorption during acid-base derangements and adrenal hormone manipulation.

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BINDING OF RADIOACTIVE ARGININE VASOPRESSIN TO V1 RECEPTORS ON PLATELETS IN PATIENTS WITH CONGENITAL NEPHROGENIC DIABETES INSIPIDUS.

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The neurohypophyseal hormone arginine vasopressin (AVP) exerts its effects through stimulation of two pharmacologi-cally distinct classes of receptors: the pressor response of this hormone and other actions, such as glyogenolysis and platelet aggregation, are mediated via vascular cal-cium-dependent (V_1) receptors, while the antidiuretic effect is mediated via cyclic AMP-dependent (V_2) receptors. Patients with X-linked Nephrogenic diabetes insipidus (NDI) are resistant to the antidiuretic action of vasopressin, most probably due to absence or defective functioning of the renal V_2 receptor. It has been proposed that V_1 recep-tors are intact in NDI patients, since they have normal pressor responses to vasopressin. However, V_1 receptors in NDI patients have never been examined directly. We per-formed direct binding studies, using the radioligand 8-arginine vasopressin, in order to characterize specific V_1 receptors on circulating blood platelets in NDI patients. The results of these studies show that the binding characteristics (maximal number of binding sites [1] and affinity for vasopressin [2]) of platelet V_1 receptors in NDI patients are identical to those in control individuals. Our data are consistent with the presence of intact vaso-pressin V_1 receptors in NDI.

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EVIDENCE OF PREDOMINANT TYPES I AND VI OF ANNEXINS IN THE PROXIMAL TUBULAR CELLS FROM RAT KIDNEY

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The annexins (type I to VII), (also called lipocortins, endonexins, calpactins),are a family of calcium binding proteins present within a wide range of tissues. Their precise functions are unknown but they are likely to play important roles in cellular regulation. Previously suggested functions are inhibition of phospholipase A2, membrane cytoskeletal linkage and control of membrane fusion events in exocytosis .They are also substrates for tyrosine and serine-kinases.
Annexins in kidney tissue are not characterized.
By using polyclonal antibodies yielded against previously purified proteins (annexins type I, II, V and VI), we determined their presence in the proximal tubular cell.
In proximal tubule preparations isolated by density gradient of Percoll solution, we found predominant types I and VI of annexins. The same results were obtained with brush border membrane vesicles (BBMV) of proximal tubule obtained by a calcium precipitation method followed by extraction of the annexins in the presence of 5 mM EGTA. The immunoreactive proteins were identified by Western Blotting after SDS PAGE.Their apparent M.W. were 67 kD and 35 kD, close to those of the already described annexins VI and I respectively.
An immunoreactivity with the antibody directed against annexin VI was also found in the urines of two patients with acute tubular diseases, but not in those of a nephrotic patient nor in those of several normal subjects. This data suggest that consistent amounts of type I and VI annexins are present in the proximal tubular cell. A close interaction with cytoskeleton is suggested by their presence in BBMV preparations. Their functionnal role is presently unknown but they potentially may take a place in the steps responsible for the expression of some tubular cell functions, such as solute transports. Modulation of these functions includes action of hormonal factors by protein phosphorylation. Annexins could be relevant substrates for the kinases linked to the brush border membrane of proximal tubular cells.

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THE PHARMACOKINETICS OF PHOSPHOCYSTEAMINE AFTER A SINGLE ORAL DOSE. W.G. van't Hoff, T. Baker, R.N. Dalton and C. Chantler.

Phosphocysteamine (PC) therapy is used to reduce lysosomal cystine accumulation in patients with cystinosis. Biochemical response is assessed by monitoring white cell cystine (WCCy) levels. The pharmacokinetics and optimal frequency of PC dosage remain to be defined.

3 boys & 4 girls with cystinosis (4 post transplant) were studied over 2 days. Ages were 2.0-16.5 yrs (mean 10.5); renal function was stable (plasma creatinines 40-192 µmol/l) at the time of the study. None were on PC nor had abnormal liver function tests. On day 1, variation in WCCy was assessed in 6 patients. On day 2, 7 patients received an oral dose of 23mg/kg PC, as a suspension. Plasma cysteamine and WCCy were measured over the subsequent 12h. WCCy was analysed using a cystine binding protein assay and plasma cysteamine by HPLC with electrochemical detection.

WCCy did not alter significantly over the pre-dose 24 h. After the PC dose, cysteamine was absorbed rapidly (peak at 30-40min) but to a variable extent (peak concn. 18-61µmol/l, area under curve 25-120). Mean t1/2 was 1.59 h (SEM 0.56). WCCy fell from a mean pre-dose level of 8.21 (1.55) to 3.23 (0.66) nmol 1/2Cys /mg protein 3 h after the dose. After 12 h, the WCCy was 5.24 (1.02). Although PC is virtually undetectable after 6 h, the WCCy levels suggest that PC may be given 12 hourly.

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PATHOLOGIC FINDINGS IN THE KIDNEYS OF PATIENTS WITH HEREDITARY TYROSINEMIA TYPE I.

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A summary of pathological changes observed in the kidneys of 23 patients with hereditary tyrosinemia Type I, seen over a 24 yr. period at the Hopital Ste-Justine, is presented. Renal tubular dysfunction, characterized by Fanconi's syndrome and hypophosphatemic rickets, is a frequent accompaniement of hereditary tyrosinemia and the kidneys of these patients, especially in the acute form, are characterized by increased weights, tubular dilatation, epithelial degenerative changes and nephrocalcinosis. Though not specific, many of these changes are reminiscent of those induced by experimental maleic acid toxicity.

Glomerulosclerosis and interstitial fibrosis were also noted in nine patients, in five of whom renal biopsies were obtained before or at the time of hepatic transplantation, accompanied by significant changes in GFR in four of the latter. Patients with hereditary tyrosinemia Type I frequently develop tubular dysfunction, especially in the acute form of the disease, but also seem at risk for chronic renal damage, calling for careful monitoring of their renal function, especially in light of the nephrotoxic effects of the immunosuprressive regimens used in transplantation.

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TOXIC EFFECTS OF CYCLOPHOSPHAMIDE/IFOSFAMIDE AND THEIR METABOLITES IN THE RENAL EPITHELIAL CELL LINE LLC-PK_1

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Cyclophosphamide (CP) and Ifosfamide are effective cytostatic agents which have been used for treatment of malignant disease in childhood for many years. Although there is an increasing number of reports of nephrotoxic side effects, little is known about the mechanisms of renal tubular damage induced by CP and IF. Thus we used the renal epithelial cell line LLC-PK_1, which is a well characterized model of tubular cells, in order to study toxic effects of CP, IF and of their highly reactive metabolites 4-OH-CP, 4-OH-IF and Acrolein. Fully confluent monolayers were incubated with the respective drugs in DMEM without fetal calf serum in order to prevent binding of the tested agent to serum protein. Total protein content of monolayers was determined at various intervals after a 1 hour incubation with 0 - 500 umoles/l of CP, IF and their metabolites. While there was no effect of CP or IF, a half maximal reduction of total cell protein was detectable at a concentration of 150 umoles/l of 4-OH-CP, 4-OH-IF and Acrolein respectively. This effect occured as early as 4 hours after the addition of the drugs. All metabolites induced a dose and time dependent reduction of RNA and of DNA synthesis. Total suppression of RNA synthesis was reached after 6 hours and/or 100 umoles/l of any of the metabolites. At the same time interval DNA synthesis was suppressed by only 50%. The results indicate that CP and IF through their reactive metabolites induce severe cytopathic effects in renal tubular cells.

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SECONDARY HYPEROXALURIA AS A CAUSE OF NEPHROCALCINOSIS IN PHOSPHATE TREATED HYPOPHOSPHATEMIC RICKETS

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In order to investigate the factors leading to nephrocalcinosis in vitamin D and phosphate treated patients with hypophosphatemic rickets clinical data of 18 patients were analysed. The mean age at the beginning of therapy was 5.8 years, the mean treatment time was 8.4 years. Six patients have developed sonographically detectable nephrocalcinosis (NC). The daily phosphate intake of patients with NC was significantly higher than that of patients with normal sonography (for both parameters $p<0.01$). There was no difference in the vitamin D dosage between the two groups. The average urinary calcium/creatinine ratio was similar in the two groups and below the hypercalciuric limit of 0.6 mmol/mmol. However the NC group had a higher incidence of hypercalciuric episodes than the group without NC (9.2 % versus 1.8 % respectively, $p<0.01$). Further urinary excretion of oxalate and phosphate was measured in 12 patients. Oxalate excretion correlated highly with urinary posphate excretion ($r=0.95$, $p<0.001$) and with phosphate intake ($r=0.93$, $p<0.001$). Young children received the highest relative doses of phosphate (range 2.27-10.8 g/day/1.73m BSA) and as a consequence their urinary oxalate excretion was highly elevated, it ranged from 0.94 to 3.38 mmol/day/1.73m BSA. Urinary oxalate excretion of untreated adults with X-linked hypophosphatemia was not elevated. It is suggested, that the high urinary oxalate excretion accompanying the high phosphate intake may be considered as a special type of enteric hyperoxaluria. Urinary calcium and oxalate excretion should be simultaneously monitored in patients with X-linked hypophosphatemic rickets treated with phosphate supplementation.

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HETEROGENEITY OF HEREDITARY NEPHRITIS

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The inheritance and the clinical pattern of 72 subjects affected by hereditary nephritis (HN) were analyzed. Criteria of diagnosis for HN were: 1)Hematuria and/or chronic renal failure (CRF) in a)at least one member in each of three generations,or b)at least two members of one generation and one member of another generation. 2)Ultrastructural renal findings of HN in at least one member of the kindred.
22 subjects(mean age 10.9 years),coming from 16 families, showed the ultrastructural renal biopsy findings of HN. Familial history and screening for hematuria made us able to identify additional 50 subjects who fulfilled the criteria of diagnosis for HN. The analysis of the 16 pedigrees lead us to distinguish various patterns of inheritance: autosomal dominant(AD) or X-linked dominant in 11 families, AD in 3 families because a clear male-to-male transmission, AD with reduced penetrance or a fresh mutation in 1 family, in the last one family both parental lines fulfilled the criteria for HN. Proteinuria was absent in 5 patients;it was < 1g/day in 10 patients;7 patients showed proteinuria > 1g/day,among them 3 showed nephrotic syndrome. At diagnosis: 4 patients showed already CRF;5 revealed at the audiometric testing neural hearing loss(NHL);3 patients showed ocular abnormalities(OA). At mean follow-up of 4.8 years: 2 additional patients progressed to CRF;2 other patients developed NHL;no further case of OA was observed.
Our study reveals and confirms the genetic and clinical heterogeneity of HN.

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MAIN CLINICAL AND BIOCHEMICAL DIFFERENCES AT DIAGNOSIS BETWEEN BARTTER AND GITELMAN SYNDROMES IN CHILDHOOD.

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We evaluated clinical and biochemical data in 24 children with Bartter-like syndromes at diagnosis to better characterize different forms of such syndromes. All patients were normotensive and presented hypokalemia(K_p < 3.0,mean 2.4± 0.5 mEq/l),high FeK(34±21%),metabolic alkalosis(HCO_3^-=31±4 mmol/l),high PRA(55±58 ng/ml/h). Secondary causes of hypokalemia were excluded. Gitelman's Syndrome(GS) was diagnosed in 7 patients:they had hypomagnesemia(Mg_p<1.5,mean 1.3± 0.2 mg%),hypermagnesuria(Mg_u/Cr_u=0.21±0.07 mg/mg),low Ca_u/Cr_u(0.041±0.024 mg/mg)and normal Osm_u(898±139 mmol/kg). Bartter's Syndrome(BS) was diagnosed in the other 17;they had hpochloremia(Cl<95 mEq/l,in 13/17 patients),hypercalciuria(Ca_u/Cr_u> 0.20 mg/mg in 11/14 patients) and/or defect of urinary concentration (Osm_u<500,mean 468±200 mmol/kg in 10/12 patients). In the BS group the incidence of hypercalciuria(79% with a mean Ca_u/Cr_u of 0.38±0.28)was the highest so far reported.
The most important clinical differences between the two groups were: 1)significantly lower age (p<0.01) in BS(2.6± 3.9 yrs,with 12/17 patients under 18 mo)compared to GS(7.8± 3.3 yrs);2)significantly lower birth weight (p<0.001) in BS (2.6±1.0 kg) compared with GS(3.4±0.4 kg); 3)hydramnios present only in 6/17 patients with BS,and tetany in 3/7 with GS; 4)the standard deviation score for height was significantly lower (p<0.05) in the BS(-2.4±2.0) than in the GS group(-0.8±0.7).

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RENAL MAGNESIUM WASTING WITH HYPERCALCIURIA. ABNORMALITIES OF ERYTHROCYTE MEMBRANE TRANSPORTS ?

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A three year old girl was referred to us for tetanic convulsions. She had hypocalcemia (1.17 mmol/l) and hypomagnesemia (0.49 mmol/l). Phosphorus and alkaline phosphatases were normal. There were no glycosuria or proteinuria. Calciuria was 1.5 mg/kg/day and the phosphorus reabsorption rate 95 %. Despite a treatment with calcium and vitamin D, the blood calcium remained low, and rose to 2.1 mmol/l after a magnesium IV load. There was no magnesium intestinal malabsorption and a supplement of 400 mg Mg++/day was started. Tetanic convulsions stopped, blood calcium level was 2.3 mmol/l, Mg level was still low and hypercalciuria (6 to 12 mg/kg/day) and hypermagnesuria (2.6 to 12.6 mg/kg/day) were disclosed. Two IV Mg loads (Rude et al.) showed a renal Mg wasting : the Tm Mg was between 0.34 and 0.87 mg/100 ml glomerular filtration rate. Acidification test by ammonium chloride showed non titratable acidity, but a high ammoniuria. Chloride fractional reabsorption was normal : 86 %. Renal ultrasound scan revealed nephrocalcinosis. Two grams of sodium bicarbonate/day were added to the treatment : the calciuria became normal (0.9 mg/kg/day) as did the magnesuria (0.4 mg/kg/day). Blood and urinary levels of magnesium and calcium of the parents and siblings were normal.
Studies were performed on the erythrocytes of this girl. The efflux of Mg was surprisingly high in a case of Mg deficiency. In contrast to reports on experimental Mg deficiency, the Na/K ATPase Mg depending pump had a high activity. Further studies are required to understand these abnormalities.

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REFERENCE VALUES FOR RENAL CONCENTRATING CAPACITY IN CHILDREN ESTIMATED BY THE DESMOPRESSIN TEST.

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Reference values are reported for maximal renal concentrating capacity in children using intranasally administered desmopressin. The results are based on 394 desmopressin tests in 374 children 0.5 to 7 years of age and 197 tests in 99 school children 11 to 13 years of age.

The concentrating capacity increased markedly during the first years of life and reached a plateau at 3.2 years of age. The mean value was 745 mosm/kg at 0.5 years of age and 1062 for children 3.2 years and older. The standard deviation was estimated to 145 mosm/kg at 0.5 years, thereafter decreasing to a constant value of 113 mosm/kg starting from 7 years of age.

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ERYTHROCYTE SODIUM-LITHIUM COUNTERTRANSPORT DETERMINATION IN CHILDREN AND ITS RELATIONSHIP TO FAMILY HISTORY OF HYPERTENSION

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Abnormalities of Na-Li countertransport (NLC) have been related to primary hypertension (HT) in adults. Normal and pathological data are limited in children. We have studied NLC in normal children and those with secondary HT (reflecting the prevalence of HT during the course of the study). In all children studied (n=56, median age 7.5 yrs, range 1.3 to 17 yrs) there was a positive relationship between body mass index (wt/ht²) (BMI) and NLC ($r=0.40$, $p<0.01$) and this was not related to age. There was no difference in NLC between normal children and those with secondary HT. We also measured intracellular sodium (iCNa) as an index of the Na pump and surprisingly observed that iCNa and NLC were inversely related, although this did not reach statistical significance.

In the normal children (n=27), there was no association between measured blood pressure and countertransport. Family history (FH) of hypertension was recorded using a five-tiered ranked score. When the lowest rank (no known FH of HT) was discarded, as this group contained an indistinguishable subgroup in whom the absence of accurate knowledge would falsely lead to a designation of a negative FH, there was a strong positive correlation between FH HT score and NLC, not related to age, BMI or BP ($n=18$, $r_s=0.50$, $p<0.05$). These data confirm that NLC is related to BMI, is not abnormal in secondary HT (as might be expected) and may genetically mark a predisposition to primary hypertension.

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LONGITUDINAL STUDY OF VARIOUS ERYTHROCYTE CATION TRANSPORT ABNORMALITIES AS AN INDEX OF SEVERITY IN CHILDREN AND ADOLESCENTS SUFFERING FROM ESSENTIAL HYPERTENSION

J.G. Mongeau, P. Mauran, G. Poirot and A. Davignon

Erythrocyte cation fluxes (ecf) were measured on fresh cells, at two different occasions, in 90 children and adolescents suffering from essential hypertension (eh) and followed for a prolonged period of time. The purpose of the study was to track the reproducibility of ecf with time and to identify if a well characterized Na transport abnormality could be an index of severity of eh.

Ninety-seven percent (97%) of patients had similar ecf results when determined at two different occasions. The patients with an increased Na-Li countertransport were the most severely hypertensive. Clinically, they presented a stable rather than labile form of hypertension. Hemodynamically, the mean arterial pressure was higher than that of the other subgroups. Finally, in those children followed for more than two years, this subgroup remained hypertensive with time. The patients with a decreased Na-K co-transport activity were second in severity; mean arterial pressure was slightly lower than the one of the previous subgroup and all remained hypertensive with time but in 4/6 patients hypertension was labile. The patients with increased Na passive permeability presented a mild form of hypertension. The patients with normal ecf seemed to form a heterogeneous group.

The conclusion is that ecf determination may be reproducible and is a useful index of severity of eh in children and adolescents.

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INCREASED RATES OF PLATELET Na^+-H^+ EXCHANGE ARE PRESENT IN BORDERLINE HYPERTENSION

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Enhanced rates of Na+-H+ exchange have been observed in platelets of adult patients with essential hypertension (EH), which suggests a role in the pathogenesis, as this may promote abnormal cell growth and vascular hypertrophy. A group of young subjects was selected as part of an on-going epidemiological study of children exposed to EH because elevated values of blood pressure found in their infancy. These patients undergo after adolescence an evaluation of the risk of EH, including study of their habitus and of their familial context in regard to the predisposition to vascular deseases. 19 of these subjects were tested for platelets Na^+-H^+ activity.The Na^+-H^+ exchange was measured using the amiloride sensitive sodium dependent component of platelet volume change under cell acidification induced by a sodium propionate medium; cell volumes were determined by electronic cell sizing (Livne *et al*, Lancet, 1987; i: 533-6).
The 19 subjects (age, years: (mean(SD)) 19.5 (2.6)) could be separated in two groups according to the presence (hypertensive group, n= 6),or the absence (normotensive group, n=13), of borderline hypertension after cardiovascular investigation including a 8 hours ambulatory registration of their blood pressure (Spacelab 5200 system). The values of systolic blood pressure at rest in the two groups were also significantly different: mmHg : 140 (20), *vs* 120 (15); SDS: 2.2(1.6) *vs* .3(1.2) respectively ($p<0.001$).
Age, sex ratio and creatininemia were not different in the two groups. The Na^+-H^+ exchange (constant rate in $s^{-1}x10^{-2}$) was significantly increased in the hypertensive group (.32 (.04) *versus* normotensive (.22 (.05)), $p < .01$) (usual values.23(.05)). Conversely, the Na^+-H^+ rates of the subjects were not different according to the presence or the absence of history of EH or severe vascular desease in their family.This results show that increased rates of Na^+-H^+ exchange are found in platelets of young subjects with borderline hypertension. This suggest that abnormality of the Na^+-H^+ exchange is present in the early stage of EH. This is potentially important to understand the later development of EH and its complications.

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INCREASED PLATELET Na^+-H^+ EXCHANGE RATES IN JUVENILE DIABETE MELLITUS

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Enhanced sodium-proton exchange may play a role in the pathogenesis of the complications of insulin dependent diabetes mellitus (IDDM). Increased rates may be responsible for excessive cell growth and be linked to the risk of vascular hypertrophy.
The Na^+-H^+ exchange was tested in children with IDDM. We used the amiloride sensitive sodium dependent component of platelet volume change under cytoplasmic acidification induced by a sodium propionate medium; cell volumes were determined by electronic cell sizing (Livne *et al*, Lancet, 1987; i: 533-6).
24 normotensive diabetic adolescents without nephropathy were studied (age (mean (SD): 14.2 (1.1) years, diabetes duration: 8.4 (2.1) years) and 21 normotensives subjects acted as control (age 24 (7.7) years). The exchange rate constants of the groups were (mean (SD) in $s^{-1}x10^{-2}$): 0.29 (0.06), 0.23 (0.05) respectively. Na^+-H^+ exchange was significantly increased in diabetics platelets compared to control group ($p<0.01$). 6 of the 24 patients with IDDM (25%) had Na^+-H^+ rates that exceeded the 97th percentile of the control group (0.33). These 6 patients were compared with the 18 patients with lower Na^+-H^+ exchange rates. They did not significantly differ in respect of their age, sex ratio and diabetes duration. The average values of microalbuminuria, of blood pressure at rest and of GFR measured with 99mTc DTPA half life in plasma were not different. The mean value of glycated hemoglobin was higher in the group of diabetics with increased Na^+-H^+ rates (12.6 (2.2) *vs* 10.4 (1.4), $p < 0.02$. The Na^+-H^+ rates also slightly correlated with an index that we use to quantify the systolic blood pressure increase during a physical exercise test on bicycle ergometer ($r=0.49$, $p<0.02$). These data show that excessive platelet Na^+-H^+ exchange may occur in the early stage of IDDM. It could be associated in certain subjects to the predisposition to hypertension and could expose to the late vascular complications of IDDM. Enhanced Na^+-H^+ exchange could also participate by this way in the development of progressive renal impairment in IDDM.

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RADIONUCLIDE NEPHROGRAPHY WITH CAPTOPRIL IN THE DIAGNOSIS OF RENOVASCULAR HYPERTENSION

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In states of reduced renal perfusion such as hemodynamically significant renal artery stenosis renal function is guarenteed by increased vasoconstriction at the efferent arteriole by the intrarenal action of angiotensin II (ANG II). Therefore, inhibition of ANG II formation with angiotensin converting enzyme inhibitors induced a reversible acute renal failure in subjects with stenosis of the renal artery in a single kidney. We studied the role radionuclide nephrography (RNG) enhanced by Captopril administration may have in the diagnosis of renal artery stenosis. We compared digital substraction angiography(DSA) and RNG (I-125 Hippuran) without and with Captopril (0.7-1.0 mg/kg orally 1 hour prior to nephrography) in 8 pediatric patients aged 2 to 17 years (median age 13 years).
Basal RNG was normal in 5 children, but Captopril induced a marked accumulation of the tracer in kidneys of 2 children, which had angiographically significant unilateral renal artery stenosis. In a 2 year old girl with a small kidney due to severe renal artery stenosis basal RNG showed reduced renal perfusion and extraction of the tracer. Captopril reduced further the tracer accumulation in the stenosed kidney. In 2 patients with reduced renal function DSA and basal and Captopril-RNG was altered only by renal insufficiency. The fall in blood pressure (median) was similar in patients with renal artery stenosis (from 130/90 to 120/70 mmHg) as in those without stenosis (from 140/100 to 130/70 mmHg).
As in adults I-125 Hippuran RNG with Captopril appears to be a useful tool to identify patients with hemodynamically significant renal artery stenosis.

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PREVALENCE OF HYPERTENSION IN THE SCHOOL POPULATION IN CATALONIA

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A group of 5.556 children aged between 4-18 years,and representative of the school population in Catalonia was studied. The sample was taken at random and stratified by ages. The level of significance was 5%. All medical and nursing staff who participated in the study weretrained and underwent audiocontrols at the beginning of the study and at periodic intervals.

The following data were obtained: height,weight,braquial and cranial permitres, elbow width,tricipital skinfold; systolic(SystBP) and diastolic blood pressure(DiasBP)(Korotkoff IV and V phases) and cardiac frequency.

1.The study of SystBP and DiasBP in relation to age and height gave the following results(prevalence for different percentiles):

	SystBP	90ºP	95ºP	97.5ºP	DiasBP	90ºP	95ºP	97.5ºP
Boys	Age	13.6	7.2	4.1		12.5	6.7	3.5
	Height	12.8	7.3	4.3		12.5	6.4	4.3
Girls	Age	12.2	6.4	3.4		13.0	7.2	3.8
	Height	12.4	6.5	3.6		11.7	7.0	4.1

2. The prevalence of hypertension was studied with the following results.

	97.5ºP		97.5ºP+10mmHg		97.5ºP+30mmHg	
	SystBP	DiasBP	SystBP	DiasBP	SystBP	DiasBP
Boys	2.10	3.84	0.81	0.27	0.19	0
Girls	2.52	3.25	0.40	0.50	0.13	0

3.Comparatively our data show higher prevalence of hypertension when compared with the curves of study of Nancy(J.L.André).

SystBP	Catalonia	Nancy	//	DiasBP	Catalonia	Nancy
Boys	3.10	2.0			3.33	2.3
Girls	3.05	2.3			3.75	2.6

4. We have not found stastically different values between IV and V Korotkoff phases.

5.In relation to obesity,the prevalence of hypertension is as follows:
90ºP : 51 ± 17.0 95ºP 35.9 ± 13 97.5ºP 23.7 ± 13

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Pathogenetic mechanisms involved in breakdown of podocyte structure in hypertrophied glomeruli in rats

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In experimental models with glomerular hypertension glomerular epithelial cells (podocytes) undergo characteristic structural alterations. The precise sequence of events leading to these abnormalities is unknown. We studied the development of podocyte injuries in hypertrophied glomeruli resulting from UNX in young rats by SEM and TEM.

The overall tuft hypertrophy includes the expansion of the peripheral glomerular capillary loops toward the urinary space and leads to the following early alterations. Podocytes apparently cannot keep up with the overall tuft hypertrophy; their processes are exposed to increased tension and are stretched out. Primary processes become extremely attenuated spanning large distances between remote capillaries. Furthermore, the outer surface of glomerular capillaries is moved toward the cell bodies of podocytes narrowing the subpodocyte space. Thereby the flow resistance for the filtrate out of the subpodocyte space into the common urinary space apparently increases followed by a rise in the hydraulic pressure in the subpodocyte space. Chronically, the increased subpodocyte pressure will bulge parts of the podocyte cell bodies toward the urinary space causing the formation of large blebs (pseudocysts). These pseudocysts increase in size and frequency with time; as shown by previous studies, they appear to be decisively involved in the development of glomerulosclerosis. In conclusion, the exposure of podocytes to increased mechanical stress, to increased tension and increased subpodocyte pressure causes the earliest structural alterations in podocytes of hypertrophied glomeruli.

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GROWTH AND GROWTH HORMONE SECRETION IN STERDID SENSITIVE NEPHROTIC SYNDROME

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Growth and endocrine function in steroid sensitive nephrotic syndrome has been studied in a recent paper*. We studied 31 boys and 11 girls taking long term steroid treatment for steroid sensitive nephrotic syndrome. Mean duration of treatment was 4,6 years (range 1 to 18 years). Mean age at diagnosis was 5,4 years (range 1,5 to 11,5) and mean number of relapses of proteinuria was 6 (2 to 23).

All the patients were treated with prednisolone : the initial steroid dosage was 2 mg/Kg/day until 1987 and then 60 mg/m2/day, for 4 weeks. The dose was tapered during 3 months and a half. Relapses of proteinuria were treated with the same corticosteroid dosage. In case of frequents relapses, maintenance steroids were given with a low dose alternate days regimen. 28 children (20 boys and 8 girls) were treated with immunossupressive therapy (chlorambucil, cyclophosphamide or mechlorethamine).

Growth was assessed by change in height standard deviation score (Δ Ht SDS) from first to last examination. There was a significant fall in the Ht SDS for the boys (ΔHt SDS -0,38, t-2,08, p< 0,05) but not for the girls. Among the 11 patients who presented an important fall in the Ht SDS (ΔHt SDS -1) there were 9 boys. Seven of them required steroid therapy until they were over 13 years. We dont find any significant correlation between ΔHt SDS and duration of treatment. This result might be explained by the high rate of immunossupressive therapy (66%) and/or by the modality of steroid therapy.

An overnight growth hormone profile study was performed in 6 boys aged 4 to 15 years with a mean ΔHt SDS of -0,87 (range 0,32, to -3,36), under steroid therapy.

Case n°	Age (Years)	Puberty (Genitalia stage)	Ht SDS	Growth Hormone (ng/ml) Mean	Pulse Number	Pulse Amplitude	Growth Rate cm/years
1	15,5	2-3	- 2	3,6	4	5,42	6,5
2	14	2	- 2	3,98	4	10,7	7,5
3	8,5	1	- 1	4,08	3	6,5	4
4	6	1	- 1,5	1,23	0	-	5
5	5,5	1	- 1,5	2,63	3	6,5	5
6	3,5	1	1	12,35	4	13,82	6

Overnight growth hormone profile was normal in two pubertal boys with growth retardation (patient n°1 and 2 with ΔHt SDS - 1,21 and - 1,04 respectively. However, the number of patients is to small to be significant.

* L.REES, S.A. GREENE, P.ADLARD, J.JONES, G.B.HAYCOCK, S.P.A. RIGDEN, M.PREECE, and C.CHANTLER.
Growth and endocrine function in steroid sensitive nephrotic syndrome.
Arch. Dis. Childh. 1988, 63, 484-490.

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EFFECT OF EARLY COMPREHENSIVE THERAPY ON GROWTH PARAMETERS IN INFANTS WITH CHRONIC RENAL FAILURE.

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In this study we evaluated the effect of comprehensive therapy (pharmacological, nutritional and dialysis) on growth parameters of twelve infant with chronic renal failure (CRF). The diagnosis of CRF was made at birth in 4 infants and in the first few months of life in other 8. All infants have been treated with early institution of nutritional therapy, providing at least 100-120 of RDA for calorie. Calorie supplement were added when intake < 80% of RDA. Pharmacological treatment was given aiming for correction of acid-base, water and mineral balance, management of renal oesteodystrophy and hypertension. Six infants were offered dialysis therapy, two of them required dialysis at birth. Growth parameters which include weight, height, head circumference were assessed periodically. Body fat stores were assessed by skinfold measurements and body proteins were assessed by measurement of midarm circumference and plasma albumin level. On follow up of a minimum one year, in six patients standard deviation score (SDS) were improved for weight, three for head circumference and two for height. Six patients their current head circumference maintained above 3rd centile and four patients their current height above the 3rd centile, two of them at the 50th centile, their current skinfold thickness (Triceps, subscapular were normal for age, their current plasma albumin levels were higher than initial level. There was no correlation between the degree of renal insufficiency and the growth velocity. We conclude that integrated and early introduction of comprehensive therapy in infants with CRF improve growth parameters, and early detection of CRF in infancy is of paramount importance.

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A PLACEBO CONTROLLED DOUBLE-BLIND TRIAL OF GROWTH HORMONE TREATMENT IN CHILDREN WITH CHRONIC RENAL INSUFFICIENCY (CRI).

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In a multicenter study we evaluated the effects of growth hormone (GH)(Norditropin R) versus placebo treatment in 22 euthyroid prepubertal patients with CRI (GFR <20ml/min/1.73m²) and growth retardation (mean (SD) height SDS:-3.1(1.1);height velocity <P25). Mean (SD) age was 9.5 (3.4) yrs; bone age 7.6 (2.2) yrs. The study duration was 1 yr. It had a double-blind, placebo-controlled design with a cross-over after 6 months. Patients were randomly assigned to one of 2 study regimens: A:GH-placebo or B:placebo-GH. Daily s.c. dose of GH (R_{DNA}) was 4 IU/m² bodysurface. Nine patients had peritoneal dialysis, 5 haemodialysis and 8 conservative treatment. Sixteen children completed 1 year study; 5 discontinued due to kidneytransplantation, 1 due to social problems. No adverse effects were seen. None of the analyzed data showed a carry-over effect. Results : (expressed as mean values)

	group A GH - plac	group B plac- GH	difference R_{DNA} GH-plac	P
Height velocity (cm/6 mo)	5.2 - 1.5	2.4 - 4.4	2.9	0.0001
ΔBone age (TW 20) (years)	0.6 - 0.7	0.3 - 0.4	0	0.90
ΔGFR (ml/min/1.73m²)	-1.9 - -0.9	-1.3 - -0.3	0	0.99
IGF-I # (ng/ml)	264 - 160	160 - 268	106	0.0001
IGF-II# (ng/ml)	1174 - 984	1190 - 1346	173	0.06
Alk.phosphatase (mMol/l)	226 - 128	192 - 302	104	0.0001
Parathyroid Horm (ng/l)	6.5 - 5.4	10.5 - 10.1	0.8	0.73

(#: Insulin-like Growth Factor-I or II)

Conclusion: GH treatment resulted in an extra height velocity of 2.87 cm /6 months (95% range:2.29-3.46), without adverse side effects.

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SURVEY OF ACCELERATED GROWTH AFTER RECOMBINANT HUMAN GROWTH HORMONE TREATMENT OF CHILDREN IN CHRONIC RENAL FAILURE AND DIALISYS TREATMENT.

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The beneficial clinical effects of recombinant human growth hormone (rhGH) in growth retarded uremic children have focused great interest. However, the cost for the whole treatment is very high and we lack sensitive parameters to survey the early response to rhGH therapy, forecast the benefits and select the subgroup of patients most sensitive to rhGH therapy.

The aim of our study was to investigate the possibility of survey over a short time (1month) the clinical and serological effects of rhGH treatment in growth retarded children in chronic renal failure (CRF), in order to obtain parameters suitable to forecast the clinical usefulness of this therapy.

Four growth retarded prepuberal children, 12.4 year-old (range 9.7 - 13.9 years) in CRF, treated by hemodialysis (2), peritoneal dialysis (1) or conservatively (1with creatinine clearance 25 ml/min), were studied over 1 month by weekly knemometry, i.e. by a sensitive device measuring the tibia lenght which is related to the total height. This measurement is very precise and accurate up to 10^{-2} mm and allows a short term evaluation of growth velocity. Moreover, children were studied by detecting with specific radioimmunoassays serum levels of endogenous growth hormone (GH) somatomedin I (IGF 1) and amino-terminal propeptide of type III procollagen (proC).

The growth velocity of the children entering the study was 2.5 (1.8-4) cm year and the mean height was 129.2 (119.9 - 138.8) cm. Both paramethers were under the third percentile for each child. There was no evidence of any role played by renal osteodistrophy and hypocaloric/hypoproteic diet on the deficient growth of these children. Over the month of baseline observation the linear tibial growth velocity, expressed by the angular coefficient of the linear regression line, was 0.036 (0.001 - 0.107) mm/day. GH peak values after arginine stimulation were 11.63 (6.7 - 15.4) ng/ml, reduced in one patient only. IGF 1 values were 1.13 (0.4 - 1.84) U.I./ml, always among normal range. ProC levels were 4.06 (1 - 8.4) µg/L, highly reduced in two children.

Over the following month, children received 4U/m2/ day rhGH subcutaneously and weekly knemometry was pursued. The mean tibial growth velocity increased from 0.036 to 0.068 (0.043 - 0.105) mm/day. It was greater than 138% in 3 children in dialysis treatment and unmodified in one, the one who was in conservative treatment. No side effects of rhGH therapy was observed.

Our study confirms the positive effects of rhGH therapy in growth retarded uraemic children in dialisys treatment, which can be early evaluated by knemometry. The timely recognition of rhGH benefits might forecast the positive long term clinical effects.

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ACCELERATED GROWTH IN CHILDREN TREATED WITH CYCLOSPORIN A ONLY, AFTER KIDNEY TRASPLANTATION.

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One of the mayor problems preventing satisfactory rehabilitation of children following successful renal trasplantation(Tx) is short stature. The most important factors responsible for the impaired growth following renal Tx seem to be the immunosuppressive therapy, especially corticosteroids, and the quality of renal function. From July'83 24 children with Tx were treated with Cyclosporin A(CyA) and low doses of Methylprednisolone (MP). MP was stopped 6 mos after Tx if renal function was normal. In 16 children (66%) this was the case. Linear growth could be studied in 13 prepubertal children(mean age 9.3±3.2 yrs), followed for at least 1 year (follow-up 1-6.9 yrs). Height was measured with a Harpenden stadiometer, every 3 mos, and bone age determined, every year, according to Tanner's formula. Growth was expressed as increment in lenght in cm/year, as height standard deviation score (HSDS) for chronologic age at Tx (To); at withdrawal of MP(T1); 6 mos (T2) and 1 year (T3) after withdrawal of MP and in the last year of the follow-up(T4). Height velocity standard deviation score (HvSDS) for bone age at T1-T3-T4. SDS was calculated according to Tanner's formula. Graft function at T1-T2-T3-T4 was evaluated by clearance of creatinine. The results can be summarized as follows:

	To	T1	T2	T3	T4
HSDS	-3.2±1.4	-3.4±1.6	* -2.9±1.7 °	-2.6±1.9	* -2.1±2.3
Growth rate cm/year		3.1±1.7	* 10.9±3.1	10.3±2.2	8.1±1.4
HvSDS		-2.9±1.9		4.3±2.2	2.2±2.5
Creat.Clear. ml/min/1.73 sm		88.6±9.4	100±21 &	86.5±9.3	85.3±9.2

*p<0.001 °p<0.01 &p<0.05

In conclusion accelerated linear growth occurs in children, also in the older ones, following successful renal Tx, treated with CyA only. This acceleration was greater in the first year after withdrawal of steroids.

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RECOMBINANT HUMAN GROWTH HORMONE THERAPY FOR CHILDREN WITH CHRONIC RENAL DISEASE. ONE YEAR EXPERIENCE OF THE BELGIAN STUDY GROUP FOR PAEDIATRIC NEPHROLOGY.

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Recombinant Human Growth Hormone (rhGH) was given to 20 renal patients. Selection criteria were : 1. height at or below the 3rd centile for age and/or growth velocity below the 25th centile; 2. pubertal signs absent or present for a maximum of one year. There were 14 boys and 6 girls, aged between 3.2 and 17.5 years.
Group A comprised 10 children (mean age 8.6 yrs), 7 with chronic renal failure (mean GFR 12 ml/min per 1.73m^2) and 3 in end stage renal failure.
Group B was made of 10 transplanted patients (mean age 12.5 yrs) with a functioning graft for at least 18 months (mean GFR 73 ml/min per 1.73m^2).
rhGH was given daily as a subcutaneous injection at a dose of 30 IU/m^2 per week.
In group A, mean growth velocity increased from 4.5 cm/yr (range 2.8 - 6.7) to 10.1 cm/yr (range 7.4 - 13.0). Height SDS improved from -3.0 to -2.5.
In group B, mean growth velocity increased from 4.0 cm/yr (range 2.1 - 6.3) to 7.3 cm/yr (range 3.7 - 8.9) with an improvement of height SDS from -3.5 to -2.9.
The average weight gain in the total group of patients was 2.0 kg/yr before and 4.1 kg/yr during therapy.
Bone age increased in parallel with chronological age.
Puberty apparently accelerated in 3 transplanted girls.
Blood glucose and glycosylated haemoglobin levels remained within normal ranges throughout the treatment period. In the transplanted patients, GFR remained unchanged.
These data confirm that rhGH is an effective and safe treatment for growth retardation in renal patients.

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EFFICACY OF RECOMBINAN HUMAN GROWTH HORMONE (rGH) IN CHILDREN WITH ESDR.

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The aim of the study was to evaluate the effect of rGH treatment in 6 prepuberal children (5M,1F) with ESRD (3 Haemodialysis and 3 predialysis with Estimated Glomerular Filtration (EGF) of 14,4±1,38 ml/m/1,73 m2 and severe growth retardation (SDS -3,008±0,6). The mean age was 10,5±3,5 y. and bone age (BA) delay of -3,74±0,9 y. Each patient received 30 IU/m2/wk of rGH (nocturnal, sbc inyection, 7 days/wk) Before rGH -- treatment the peak GH response to stimulation (insulin-hypoglycemia) was 5,66±7,99 ng/ml.
RESULTS (Mean and SD):

	-12 m	+6 m	+12 m	T.Student
BA/Years	7,16±2,54	7,4±2,7	7,58±2,85	NS
Tanner/Stage	1,33±0,51	1,5±0,77	1,66±1,03	NS
Height (SDS)	-3,008±0,6	-2,76±0,5	-2,2±0,5	P<0,05
Arm Circunf(AC)%	89,8±10	89,3±8	93±6	NS
Triceps Skinfold %	79,6±23	68,5±19	71,5±24	NS
Nutritional Index %	89±13,8	86,8±11,8	85,5±13,6	NS
EGF ml/min/1,73	14,4±1,38	11,4±1,8	10,6±1,34	P<0,05
Intact PTH(N<40ng/ml)	41,8±43	85,5±104	167±330	NS
Alcaline Phosph(AP)U/L	328±291	471±141	532±191	NS
IGF$_1$ (U/ml)	1,8±1,01	4,76±2,3	5,06±3,4	P<0,05
HB$_1$C %	5,28±0,87	5,36±0,8	5,73±0,77	NS

The height velocity (HTVEL) during the 1 year on treatment was 9,38±2,67 cm. and 162% of HTVEL for BA.
CONCLUSIONS:
A significant increase of growth was achieved in stunted - children with ESRD (Predialysis and dialysis), with supra-physiological doses of rGH, without acceleration of bone - age and with a significant increase in IGF$_1$ levels.
Antropometric measurement indicates an increase in AC and decrease in TSF not significant. There was a not significant increase of AP and iPTH that may be related to growth. EGF decrease may be due to increase in S Creatinine for muscle mass increase.

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RENAL AND HORMONAL RESPONSES TO SOMATOSTATIN

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Effects of somatostatin (Stilamin^R, Serono) (250 ug bolus, followed by 250 ug/h continuous infusion for two hours) on renal hemodynamics, electrolyte- and water handling, urinary excretion of catecholamines and prostaglandins as well as on plasma concentrations of various vasoactive hormones was studied in 7 normal subjects. Somatostatin decreased C_{PAH} (679±13 vs 248±46; $\bar{x}$ ± SEM), C_{IN} (131±13 vs 50±11), urine volume (3.6±0.8 vs 1.3±0.4 ml/min per 1.73m^2), osmotic- and free water clearance, Na-excretion (340±76 vs 168±38 umol/min/1.73m^2), K-excretion, while Uosm and P-excretion increased significantly. Plasma concentration of vasopressin (AVP), atrial natriuretic factor, noradrenalin (NA), adrenalin (A), dopamine (DA), remained unchanged, while plasma renin activity (3.0±0.2 vs 2.4±0.2 ng/ml/h) and glucagon level (40±11 vs 20±16 pg/ml) decreased. Urinary excretion of NA, A, and DA as well as PGE2 and PGF2alpha were suppressed under somatostatin. A significant positive correlation was found between urinary DA and Na-excretion (r=0.7; p < 0.001), and urinary PGE2 and GFR (r=0.52; p < 0.01). Without accompanying changes in plasma osmolality and AVP concentration a significant antidiuresis was shown (decreased free water clearance and increased urine osmolality) which suggests a direct antidiuretic effect of somatostatin. Our results show that somatostatin exerts important effects on the kidney. Changes are due partly to decreased renal plasma flow but interaction of glucagon, PGE2 and DA may also play a significant role in this.

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BONE MINERAL STATUS AND GROWTH IN CHILDREN WITH STEROID-DEPENDENT NEPHROTIC SYNDROME (SDNS)

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The purpose of this study was to assess bone mineral content and growth in children with SDNS and to evaluate factors that influence them. Using photon absorptiometry 54 measurements of bone density (BD) were made in the forearm of 31 children treated for 1711 months in total. All patients had normal serum creatinine. Values of BD were compared with those of appropriate age- and sex-matched controls. Patients were divided in those receiving a total dose of prednisolone (PR) <0.7 mg/kg/48hrs (group 1) and ≥0.7 mg/kg/48hrs (group 2).
There was a significant difference in sds of BD (-0.2 ± 1.1 and -2.3 ± 1.8 p <0.001) and of height (0.03 ± 0.9 and -1.3 ± 0.9 p <0.02) between groups 1 and 2. In addition Δsds/year of BMC and height were lower in group 2 (p <0.01 and 0.05). The duration of treatment correlated with BD and height sds (R=0.55 and 0.51, p <0.01). Significant demineralization (BD <-2 sds) was found in 37% of children on PR for ≥4 years and and in 20% treated <4 years. Severe decrease of BD (<-3 sds) occurred in 19% and 7% of patients respectively. Only 9.6% of children had significant and 6.5% severe growth retardation, all were on PR treated for >6 years. BMC and height correlated significantly (R=0.4, p <0.02).
In conclusion BD was decreased in 29% of children with SDNS, however only 13% had severe demineralization. This problem was more frequent in children with long term treatment with a relatively high dose of PR. The PR regimens used had a negative effect on the height of few patients, possibly by decreasing bone mineralization.

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MICROALBUMINURIA IN PATIENTS WITH REFLUX NEPHROPATHY (RN)

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Microalbuminuria (MA) was studied in 145 patients with RN (groups 1 and 2) and in 46 normal controls.
Group 1: 74 patients aged 11.5-25.7 (mean 19.66) years studied at the 10 year follow-up review of a cohort of children who were part of a long term prospective study on the relationship of renin and blood pressure in RN.
Group 2: 71 younger patients aged 3.6-16 (mean 10.36) years who subsequently attended the Hospital in addition to Group 1.
All patients had normal renal function and were not on antihypertensive treatment.
24 hour urine samples were collected and albumin excretion was measured by RIA and expressed as urine albumin creatinine ratio (UA/UC) (mg/mmol). The UA/UC was above the normal range (0.06-2.50) in 15/74 (20.3% of Group 1) and 13/71 (18.3% of Group 2). The mean UA/UC of both Group 1 and 2 (0.94 and 1.01) were significantly greater than the mean of the normal group (0.33; $p<0.001$) but there was no significant difference between the older Group 1 and the younger Group 2. There was no correlation between UA/UC and plasma creatinine, blood pressure, plasma renin activity or mean sodium excretion in all groups studied but there was a significant correlation between UA/UC and the degree of scarring in Group 2 but not Group 1.
MA therefore occurs in RN but in our study did not appear to be clearly related to duration of scarring and only correlated with the degree of scarring in younger patients.

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PROTEINURIA AND BRUSH-BORDER ANTIGENS IN REFLUX NEPHROPATHY. Ginevri F.,*Mutti A.,Ghiggeri G.M.,*Alinovi R.,Perfumo F., *Bergamaschi E.,Gusmano R.

Proteinuria was characterized in 82 children affected by various grades of reflux nephropathy(RN). The urinary excretion of high (albumin) and low (RBP,β2-microglobulin) molecular weight proteins and of brush-border antigens(BBA) revealed by monoclonal antibodies was taken as an index of glomerular and tubular cell dysfunction respectively.
All such markers were increased in RN children with different distributions among subgroups in relation to the renal function and the grading of RN. Patients who had depressed values of GFR showed very high levels of albuminuria,low molecular weight proteinuria and BBA,all these variables being correlated. Only microproteins but not albumin and BBA were increased in children with normal renal function indicating an isolate tubular defect which does not involve the proximal segment of the tubule. Increased microprotein concentrations in urine were correlated with the age of children but not with the grade of reflux nephropathy as determined by radioisotopic technique.
These results demonstrate the presence of either tubular or glomerular alterations in children with advanced grades of nephropathy whereas only signs of tubular alterations were found in subjects with normal renal function. The normality of urinary BBA in this phase excludes the presence of alterations involving tubular cells in the proximal segment of the tubule containing the brush border.
The clinical usefulness of low molecular weight protein determination in RN must be further addressed.

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PERIURETHRAL PH AND LACTOBACILLI IN NEWBORN GIRLS - A TEMPORARY DEFENCE AGAINST URINARY TRACT INFECTION?

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UTI is more common in girls than in boys, except during the first month of life, when girls seldom get UTI. Our hypothesis is that the maternal hormonal influence temporarily makes the periurethral area more resistant against colonization with uropathogens and ascending infection. This study investigates periurethral pH and bacterial flora, especially lactobacilli in newborn girls.

Material: 35 girls were repeatedly investigated (mean 3 samples) during the first week of life, 12 girls were followed during the first month.

Method: Periurethral pH was examined with a glass surface electrode. Periurethral bacterial samples were cultured anaerobically on blood agar and Rogosa agar, selective for lactobacilli. Further identification was performed with gas-liquid chromatography.

Results: Periurethral pH day 1: 5.8 (±0.4); day 2-10: 5.4 (±0.6) ($p<0.01$); day 10-30: 6.7 ($p<0.01$) (the latter pH level then constant until puberty).
Lactobacilli were isolated from 28 of 35 girls. The colonization was fully developed after 3-4 days, and then gradually diminished after 2 weeks. The total anaerobic flora was examined in 8 girls, lactobacilli were present in 6 girls and predominated in 5 girls. E.coli were present in scanty amounts in 50% of girls on day 4, no correlation was found to the lactobacilli colonization.

The study showed that newborn girls have a distinctive periurethral ecology as compared to older girls.

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ANTIBIOTIC SUSCEPTIBILITY OF THE PERIURETHRAL NORMAL FLORA IN VIVO AND IN VITRO IN HEALTHY GIRLS

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The periurethral (PU) normal flora is believed to be an important host factor preventing colonization with potentially uropathogenic enterobacteria. Earlier data show that antibiotic treatment might precede UTI. This study investigates: 1. In vitro antibiotic susceptibility of the predominant PU anaerobic flora. 2: In vivo effects of amoxicillin (amox) and trimethoprimsulphamethoxazole (TMPs) on the normal PU flora.

Material and methods: 1: Sixtyfour anaerobic isolates from 21 healthy girls (3-13 yrs) were tested for susceptibility to 9 different antibiotics including amox and TMPs with agar dilution technique. 2: Eighteen healthy girls (3-10 yrs) were treated perorally either with amox (N=8) or TMPs (N=10) for 5 days. The PU anaerobic and aerobic floras were quantitatively assessed and characterized before, during and 3 weeks after treatment.

Results: PU anaerobes were highly susceptible in vitro to several antibiotics including amox but to TMPs. During treatment with amox, a reduction in total counts and composition of the anaerobic flora occurred in 5/8 girls, and a heavy colonization with enterobacteria appeared in all 8 girls. After treatment, a complete normalisation to the pretreatment status was registered. No effects on the PU flora was seen during treatment with TMPs. Our data support the hypothesis that antibiotics might disturbe PU ecology and thus be one factor in the pathogenesis of UTI.

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DMSA SCANNING IN ACUTE URINARY TRACT INFECTION (UTI) AND IT'S RELATIONSHIP TO VESICO URETERIC REFLUX

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78 consecutive children aged 0.05-14 years (mean 4.1 years) with a proven UTI underwent 99Tc Dimercaptosuccinic Acid (DMSA) scans within a week of presentation. 28 children with 33 abnormal kidneys on initial scan were rescanned 3-18 months later. Micturating cystograms were done on all children with abnormal scans, and if clinically indicated. All patients underwent ultrasonography and plain abdominal x-ray.

39 children (46 kidneys) had abnormal initial scans and 39 children had normal first DMSA scans. Of the 33 abnormal kidneys rescanned, 14 had returned to normal. 12 kidneys showed improvement in abnormalities and in 7 the scan was the same or worse. 13 initially abnormal kidneys have not yet been rescanned.

Vesico ureteric reflux (VUR) was present in 19 out of the 46 initially abnormal renal units. However it was only present in 5 of the 14 kidneys in which the initial scan showed complete resolution (36%). 10 out of the 19 kidneys which were persistantly abnormal at 3 months had VUR (52%). In those kidneys in whom the initial scan was normal (n=110), 80 renal units were examined for reflux and it was present in 17 (21%).

Renal involvement is common in UTI and most abnormalities will improve (79%). Only 43% resolved. The abnormalities are commonly present without VUR, particularly in the group showing complete resolution (64%). Caution in interpreting DMSA scans done near the time of infection should be exercised as the abnormalities may be transient. The significance of these acute changes remains to be seen.

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99-Tc-DMSA SCINTIGRAPHY IN ACUTE PYELONEPHRITIS IN CHILDREN.

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Acute pyelonephritis (APN) in children is a serious disease that can result in a permanent renal damage. Therefore a correct and early diagnosis is of utmost importance. So far the diagnosis has mainly been based on unspecific parameters such as fever, elevated sedimentation rate (ESR) and acute phase reactants (CRP). The aim of the present study was to evaluateTc-DMSA as a more specific diagnostic tool.

All children admitted to the hospital with APN were studied after informed consent. 34 children, 2 boys and 32 girls, 0.2-15.9 (median 1.0) years of age, with APN defined as fever >38.5°C, ESR >20 mm/h or CRP >20 mg/ml and positive urine culture, were studied. Ultrasound (US) examination (with regard to obstruction, echogenicity and volume) was performed within the first 3 days, Tc-DMSA scintigraphy (DMSA) (with regard to defects in renal uptake and size) and DDAVP test within the first 5 days. The defects in DMSA uptake were graded from 0-2 (0 = normal). Two months later 18 patients were examined with i.v. urography (IVU), micturition cystourethrography (MCU), US, Tc-DMSA and DDAVP.

Results: 3/33 children had a CRP<20 mg/ml but an elevated ESR (22, 48 and 59 mm/h). ESR varied between 6 and 85 (mean 34) mm/h. Mean max. urine osmolality in the acute phase was 550 mOsm/kg significantly lower than after two months (mean 757 mOsm/kg). At US one obstructed kidney was found. Changes in echogenicity were observed in 8 patients (9 kidneys) in the acute phase but no changes were seen after 2 months. 31 patients (47 kidneys) had defects in uptake at the acute DMSA (22 kidneys grade 2, 25 kidneys grade 1). All 9 children with US changes had DMSA grade 2 changes. CRP was related to the grade of DMSA changes (mean CRP was 18 in grade 0, 74 in grade 1 and 134 mg/ml in grade 2).

At the 2 months follow up, all patients had improved at DMSA, but 50% had persistent DMSA changes. US and IVU showed no changes except for the obstructed kidney. Three of 18 investigated children had vesicoureteric refluxes (VUR) in 6 kidneys. All 4 kidneys with VUR ≥ grade III/V had DMSA grade 2 changes at the first investigation.

Conclusions: 31/33 patients showed defects in DMSA-uptake at the acute phase of APN indicating that DMSA is of great value in the diagnosis of APN in children.

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DMSA SCAN IN ACUTE INFECTIOUS PYELONEPHRITIS IN 150 CHILDREN

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Acute infectious pyelonephritis (APN) documented by urinary tract infection, fever >38°5, leucocyturia and inflammatory syndrome occured in 150 children (1 m. to 15 y. old, mean 4 y ; first APN episod in 2/3 of them). They have been investigated by quantitative DMSA scintigraphy. The results have been compared to sonography, IVP, cystography and urinary concentration test (DDAVP).

DMSA abnormalities were found in 48 % of examined kidneys. Three patterns have been observed : decreased fixation (84 %) frequent at the early phase, heterogeneous fixation (41 %) or polar defect (50 %).

The correlations with the clinical symptoms or with the other tests were poor ; DDAVP, sonography and IVP remained within the normal range in most of them. The correlation with the presence of an uropathy, mainly vesico-ureteral reflux, was better. DMSA abnormalities wase observed in 81% of the kidenys with an uropathy ; however 39 % of "normal" kidneys whithout any uropathy exhibited also DMSA abnormalities. The follow up of 50 altered scans (6 months to 2 years) has shown an improvement in 50 %, a total recovery in 25 %, or a permanent DMSA defect in 25 %.

These results stress out the good sensitivity of DMSA scan at the early phase of APN in children, able to separate an acute pyelonephritis from an acute infectious pyelitis.

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^{99m}Tc-DMSA SCINTIGRAPHY AS DIAGNOSTIC TOOL IN ACUTE PYELONEPHRITIS

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We recently, in experimental studies, documented that areas of acute pyelonephritis (PN) in the cortex will exhibit decreased DMSA uptake (Ped Nephrol 1990). In the present study ^{99m}Tc-DMSA scintigraphy (DMSA) was performed within one week in 24 children (18 girls and 6 boys) with acute PN. Nineteen of them had areas of decreased isotope uptake in one (12/19) or both kidneys (7/19). These children were compared with 10 children with a history of recurrent urinary tract infections (UTI) and renal scarring. The changes on DMSA looked the same in the two groups of patients. However, the total isotope uptake was evenly distributed between the kidneys in acute PN, while it was distributed in accordance with the parenchymal loss in scarred kidneys. This may be useful in the differentiation between acute PN and scarred kidneys on DMSA. On ultrasound 10/24 children had local parenchymal changes, swollen kidneys or slight dilatation of the pelvis. When the ultrasound investigation was repeated after six weeks most changes were normalized. In 5/20 children investigated with micturation urethro-cystography vesico-uretheral reflux was found. Urine albumin/creatinine and NAG/creatinine quotients were increased in the early course but decreased successively on repeated investigations and were normalized at six weeks.

^{99m}DMSA scintigraphy is a reliable method in the diagnosis of acute PN and in most cases the changes can be differentiated from scarred kidneys. In less than 50% of the patients the acute renal changes were seen on ultrasound. Functional parameters may strengthen the diagnosis.

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RARE-MR-UROGRAPHY
A New Urographic Method

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Methods: RARE-MR-Urography (**R**apid **A**quisition with **R**elaxation **E**nhancement) is a new T2-weighted magnetic resonance technique for rapid visualization of fluid compartments. By a simulateously performed T1-weighted exposure an image of the topography of the urinary tract in relation to the surrounding anatomy can be produced. 12 newborn infants and 8 older children with malformations of the urinary tract were examined. The diagnoses were: urethral valves, vesico-ureteral-reflux, subpelvic obstructions, ureter duplication with ureterocele or ectopic ureter, obstructive megaureter, cystic kidney, and renal megacalicosis. Three of the children had a reduced renal function. Most of the malformations in newborns were diagnosed prenatally by sonography. In one case a prenatal RARE-examination was performed in the 34th week of gestation.

Results: Due to the short exposure time of 27" most examinations could be performed under promazine sedation. No contrast media or radiation is necessary. The images received resemble those got by conventional technique. Even in cases previously shown to be unvisible by conventional urography due to kidney dysfunction or obstruction the urinary tract could be visualized clearly by this technique. As the urinary tract is shown in its whole extension, a topographic evaluation of extended malformations is more distinct compared to ultrasonography.

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RENAL HEMODYNAMIC RESPONCE TO A LOW PROTEIN DIET IN TRASPLANTED KIDNEY.

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It is reported that a low protein diet may reduce the glomerular filtration rate (GFR) and renal plasma flow (RPF) in subjects with normal kidney function and also in patients with variable degrees of kidney failure.There are no comparable data in trasplanted(Tx)patients.The aim of this study was to evaluate the effect of two different diets on renal hemodynamic in Tx adolescents.For this purpose 8 adolescents,4 girls and 4 boys,mean age 18±2.6 yrs,Tx from 5.1±2.3 yrs,were studied.Immunosuppressive therapy consisted of methilprednisolone(0.15±0.05 mg/Kg/d)and either azathioprine (2.1±0.28 mg/Kg/d)or cyclosporin A(8.2±0.86 mg/Kg/d).After their usual protein diet(1.88±0.31 g/Kg/d) (NPD) and after two weeks of isocaloric diet but with 50% of NPD(0.87±0.12 g/Kg/d) (LPD) (NPD vs LPD:$p<0.01$)we evaluated,in all patients,the protein intake by the last three days records and urea excretion;GFR(C INU);RPF(C PAH) and plasma renin activity (PRA).Our patients were further divided according to their GFR in:group A (3 subjects) GFR>70 ml/min/1.73sm;group B(5 subjects)GFR<70ml/min/1.73sm The results are summarized:

		NPD	LPD	Δ	
GFR ml/min/1.73sm	A	107±30	75±20	32±26	*
	B	42±17	38±16	4±5	
RPF ml/min/1.73sm	A	459±115	337±86	122±90	*
	B	212±98	191±97	22±25	
PRA ng/ml/h	A	11.5±4.55	6.8±7	4.67±2.5	°
	B	5.83±8.8	4.66±7.2	1.22±1.7	

*p = 0.05 , °p = 0,056 by Student's t test for paired data

In conclusion our data suggest that the effects of LPD on renal hemodynamic are more evident in Tx kidney with GFR>70 ml/min/1.73 sm than in those with chronic renal trasplant failure.

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CT HEAD SCAN APPEARANCE AND HEAD SIZE IN INFANTS WITH CHRONIC RENAL FAILURE WHO RECEIVED EARLY COMPREHENSIVE THERAPY.

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Earlier reports revealed that chronic renal failure (CRF) in infancy can lead to profound neurological abnormalities associated with microcephly, evidence of brain atrophy on CT scan and progressive encephalopathy.It was suggested that institution of early comprehensive therapy and no aluminium salt policy may be crucial in obtaining a more favourable outcome. In this study we evaluated the effect of early comprehensive therapy (pharmacological nutritional and dialysis) and a policy of no aluminum salt on the brain growth and in preventing the profound neurological abnormalities in Twelve infants with CRF.The diagnosis of CRF was made at birth in 4 infants and in the first few months of life in the other 8.All infants have been treated with early institution of nutritional therapy.Pharmacological treatment was given aiming for correction of acid-base, water and mineral balance, management of renal oesteodystrophy and hypertension. Six infants were offered dialysis therapy, two of them required dialysis at birth. None of these infant received aluminum salt, only calcium carbonate as phosphorous binder was given. During the period of observation serial measurements of head circumference were obtained,unenhanced CT brain scans were carried out at least one year after diagnosis of CRF. On follow up the head circumference of all patients were above the 3rd centile except in two patients where the head circumference were >2SD below the mean. The CT brain scan was abnormal in only one patient with evidence of brain atrophy. None of our patients developed recurrent seizures, or progressive encephalopathy and their neurological examination were normal.

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CHRONIC PERITONEAL DIALYSIS (CPD) IN CHILDREN: A MULTICENTER CLINICAL STUDY

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The Italian Registry of pediatric CPD, which collects data of patients under 15 years of age at the start of dialysis, was set up in 1986. The number of participating pediatric nephrological centers increased from 7 in 1986 to 11 in 1988 and the total number of patients enrolled in the Registry was 70. CPD was the first-choice therapy in 77% of the patients. Data on 89 catheters,surgically inserted,were collected;the complications observed during 1417 dialysis months numbered 70 in total (1:20.8 dialysis-month). Actuarial catheter survival was 92.7%, 84.8% and 68.8% at 6,12 and 24 months respectively. 24/89 catheters were removed:infection (19) was the main reason. The incidence of peritonitis episodes changed from 1:10.9 patient-months in 1986 to 1:19.8 in 1988.The majority of the cultured organisms were Gram positive bacteria, mainly Staph. aureus and epidermidis. The duration of CPD was 21.4±16.7 months; 37/70 patients ended CPD during the observation period (renal transplantation 24, shift to hemodialysis 5,recovery of renal function 2, death 5). The patient survival was 98.5% at 6 months and 92.5% at 3 years,while the technique survival at the same times was 97% and 84% respectively.

The interest of these data lies not only in the high number of patients and the long follow-up, but also in the fact that they come from many dialysis centers, differing in size, organization and experience.

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RECOMBINANT HUMAN ERYTHROPOIETIN (rHuEPO) STIMULATES TESTOSTERONE PRODUCTION ON ISOLATED ADULT RAT LEYDIG CELLS.

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Erythropoietin (EPO),a glycoprotein considered a growth factor,corrects anemia of renal patients.These patients improve their sexual functions after EPO treatment.Recent evidences demonstrated that several growth factors act ,through specific receptors,on Leydig cells influencing steroidogenetic activity.The aim of our study is to verify if EPO may also be involved in the mechanisms regulating Leydig steroidogenesis.We have therefore evaluated the effect of rHuEPO on testosterone secretion by isolated adult rat Leydig cells. Aliquots of high purified rat Leydig cells (90%-92%),by Percoll discontinuous gradients,were incubated in M-199with L-glutamine, Hanks'salt,BSA 0.2%,at 34°C in controlled atmosphere($pO_2$95%-$pCO_2$5%),in shacking bathroom(90 cycles/min.),in sterile polyethylene tubes containing rHuEPO at the doses ranging from 50 mU to 50 U/ml.After 3h the incubation was stopped and tubes were immediatly centrifuged 1500g/15min. and supernatant was stored at -20°C until testosterone assay by RIA method. rHuEPO exerts a significative($p < 0.05$) stimulatory effect on testosterone secretion starting at the dose 1.0 U/ml,with a maximal stimulatory effect at the dose of 10.0 U/ml (6.8±1.2 ng/2x10^{6}cells/ml/3h versus control : 3.5± 0.7).

Conclusions:Our preliminary data show,for the first time,that rHuEPO influences rat Leydig steroidogenesis enhancing testosterone production. These results suggest that EPO therapy could improve sexual function involving also Leydig steroidogenesis.

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3-METHYLHISTIDINE URINARY EXCRETION IN UREMIC INFANTS.

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3-Methylhistidine (3-MH) is an aminoacid that is formed by the methylation of histidine in actin and myosin and is not formed to an important extent in tissues other than muscle. After releasing, it is not reutilized for protein synthesis, is not involved in other metabolic processes and is excreted in urine unchanged. These features provide enough reasons to use 3MH as an index of muscle protein breakdown (and therefore of the whole anabolic/catabolic status), in subjects with good renal function where urinary excretion is an expression of its production. In uremic patients, in whom 3MH excretion is impaired, the 3MH/creatinine (creat) ratio is theoretically a better index. The need for a meat free diet, and for 24-hour urine collections,make the use of 3MH difficult;this explains,at least to some extent,the absence of data in literature concerning children with chronic renal failure (CRF). The aim of this study was: 1) to evaluate urinary 3MH and 3MH/creat ratio in uremic infants with stable renal function; 2) to determine if 3MH excretion in a single timed voiding is representative of that in the whole 24-hour excretion and 3) to see the effect of catabolic stress on these parameter.

Material and Methods: - 20 24-hour urine collections were obtained in 4 infants with severe CRF (average GFR = 11 ml/min/1.73 sqm, range 5-17) mainly due to urinary tract malformation requiring urinary diversion, on conservative treatment, and a meat-free diet. Bags were emptied every three hours and urine was kept in a refrigerator (+ 4° C). At the end of the collection, a sample of the whole collection was frozen (- 20° C). In the meantime dietary intake was carefully recorded. In 12 cases, a 3-hour specimen was collected separately to evaluate a correlation with the 24 hour total excretion. 21 more 24-hour collections were obtained from 2 children, following surgical stress for an intervention on urinary tract, for 14 and 7 days respectively. Their GFR was 10 and 92 ml/min/1.73sqm.

Results: Average 3MH/creat ratio was 0.32 (SD=0.12, range 0.17-0.59). (Normal from the literature < 0.2). Mean energy intake was 99% RDA (SD 16.7; range 75-132) and mean protein intake 101% RDA (SD 36; range 50-158). Urinary 3MH excretion in 3-6 hour sample correlated very well with that in 24-hour urine collection (r=0.87). During catabolic stress, the 3MH/creat ratio increased from 0.2 to a peak value of 0.67 in the infant with renal impairment; in the child with normal GFR ratio raised from 0.28,in the first day after intervention, to a peak value of 0.5.

Conclusion 1) Urinary 3MH/creat ratio is well above normal value in uremic children 2) 3MH in 3-6 hour sample seems well correlated with total daily excretion 3) 3MH urinary excretion increased significantly after acute stress (surgical intervention and fasting) in an infant with CRF, as did in another with normal GFR.

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SEVERE NEUROLOGICAL SYMPTOMS AFTER RENAL TRANSPLANTATION A-B. Bohlin, U. Berg, M. Englund, A. Persson, G. Malm, A .Tibell, G. Tydén

Severe complications from the central nervous system (CNS) occurred in seven of 36 children (19%) after renal transplantation (tx). The children, aged 1.6-13.1 years at tx, exhibited seizures (5), drowsiness (5), confusion (4), visual disturbances (1), and mental changes (1) 1-136 (median 12) days after tx. All children were on cyclosporin and prednisolone therapy, six of them had azathioprine as well. One child had antirejection therapy with iv solumedrone. Five patients had antihypertensive therapy, but only one had significant hypertension at the time of the CNS symptoms. In 6/7 children the cyclosporin trough blood levels were within the therapeutic range; one had a high level. Blood glucose and electrolytes were normal, and virology tests were negative. The EEGs showed diffuse abnormalities in all cases, and epileptic activity in two. The cerebrospinal fluid was normal in 4/5 children, one had elevated protein concentration. CT scans of the head showed brain atrophy in 5/6 children, interpreted as being caused by the long-standing chronic renal failure. One child had white matter lucencies. In five children the CNS symptoms disappeared spontaneously within 24 h and they had no further neurological symptoms during 4-37 months of follow-up. One child had a relapse after two months and she has sequele consisting of fits, mental status changes and subnormal intellectual function. The seventh child died in pancreatitis.

Conclusion: Serious neurological complications are not uncommon after renal transplantation in children. They often seem to be reversible, but sequele may occur. Cyclosporin might play an etiological role,since there are several other reports about its neurotoxicity. However, many other factors might also be contributory: hypertension, corticosteroids, other neurotropic drugs, rejection, electrolyte disturbances and as yet unknown factors.

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TREATMENT OF HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA (FHC) BY PLASMA EXCHANGE (PE) AND LIPOADSORPTION (LA)

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For 4 years, we have been treating two non related girls presenting type II homozygous FHC. We compared different treatments : PE by cytocentrifugation or filtration (with or without reuse of the filters) and LA on dextran sulfate columns (Liposorber Kaneka) of varying frequency (one session a week or one every two weeks). We assessed the long term results of the methods by the blood levels before sessions and the efficiency of each session by the differences between blood levels before and after.

For patient n°1, there was non difference in total cholesterol (TC) before sessions during PE ou LA (15.0 ± 1.5 vs 15.4 ± 0.9), nor in triglycerides (TG). But the level of HDL cholesterol was higher during LA (0.8 ± 0.1 vs 0.4 ± 0.1) and the apolipoprotein B (apo B) lower (3.6 ± 0.2 vs 4.4 ± 0.6) as was the ratio B/A. During LA, both the IgG and the hemoglobin (Hb) levels before session were higher (7.3 ± 1.5 vs 5.5 ± 0.8 ; 13.2 ± 0.6 vs 12.4 ± 0.6 respectively). LA had greater effect than PE on TC (12.6 ± 0.7 vs 10.7 ± 1.4), but both was equally effective on apo B and TG. In PE the reuse of the filters did not affect the results. In LA, the one session a week schedule gave better results than one session every two weeks as evidenced by the TC (11.4 ± 1.7 vs 15.4 ± 0.9), the LDL cholesterol (9.2 ± 1.8 vs 13.8 ± 0.7) and the TG (0.7 ± 0.3 vs 0.9 ± 0.2) before session.

For patient n°2, the long term results were the same in PE by cytocentrifugation or by filtration despite a greater efficacy of the filtration sessions. The comparaison PE/LA allowed the same conclusions as in patient n°1. The reuse of the filter in PE and of the first filter in LA diminished the efficacy of both methods.

In conclusion, LA led to a greater specificity of treatment (lowering of LDL cholesterol or apo B and preservation of HDL cholesterol), but the blood levels before session were the same as those obtained by PE, probably because of the long interval between two sessions. IgG and Hb were well preserved by LA. The rythm of one session a week gave better results in LA. In PE, filtration was more effective than cytocentrifugation. The reuse of the filters is of little interest in both methods.

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WHAT IS THE SIGNIFICANCE OF SERUM ANTITHYROID ANTIBODIES IN ALPORT'S SYNDROME?

S. De Marchi and E. Cecchin.

The purpose of this study was to investigate the significance of serum antithyroid antibodies in Alport's syndrome (AlpS). Thyroid microsomal (TMA) and thyroglobulin (TgHA) antibodies were assessed in 3 families with AlpS for a total of 11 patients, in 40 hemodialysis (HD) patients and in 40 healthy subjects (HS). Thyroid function tests including the measurement of serum total thyroxine (TT_4), total triiodothyronine (TT_3), free thyroxine (fT_4) and free triiodothyronine (fT_3) concentrations, and the thyrotropin-releasing hormone (TRH) stimulation test were performed in all patients and subjects. Among patients with AlpS 5 (45%) had high titers of TMA and 8 (73%) had positive titers of TgHA. The fine-needle aspiration biopsy of the thyroid demonstrated a lymphocytic infiltration of the gland in all 5 patients with high TMA titers, thus confirming the existence of asymptomatic autoimmune thyroiditis. The prevalence of antithyroid antibodies in HS and HD patients was 7.5 and 12.5% respectively. Functional tests demonstrated a thyroid dysfunction in 4 of 5 patients with AlpS and asymptomatic autoimmune thyroiditis. Two patients had evidence of subclinical hypothyroidism. Two other patients, both with end-stage renal disease, showed blunted TSH response to TRH, increased fT_4 and high borderline levels of fT_3.
In conclusion, the present study indicates that high titers of serum antithyroid antibodies may be detected in patients with AlpS. These patients are at risk to have asymptomatic autoimmune thyroiditis and thyroid dysfunction. Subclinical hypothyroidism and, perhaps, preclinical hyperthyroidism may be found in these patients.

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NEPHRITIS, HEREDITER PLATELET DISORDER AND DEAFNESS: *EPSTEIN SYNDROME*

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A 14 years old boy was studied with persistent proteinuria (1.6-4.0 g/day), microscopic hematuria, moderate hypertension, macrothrombocytopenia (giant platelets, platelet number 5000--30000/µl) and a familial sensorineural hearing loss (the father and the brother were also affected). Ultrasonography showed a unilateral soliter cyst in the kidney.Kidney biopsy presented a diffuse mesangial proliferation, and a focal thickening of the glomerular basement membrane was seen on electronmicroscopy. With bone marrow aspiration a decreased number of megacaryocytes was observed. The aggregation response of the platelets was decreased on collagen, epinephrine and ADP but it was normal on aggristin. The number of platelets was slightly diminished with a normal size in both parents and the brother, and showed a decreased aggregability on collagen, epinephrine and ADP in the case of his brother and mother. Regarding the father no functional abnormality of platelets was observed. Urinalysis and kidney function was normal in the family members. The presented case with nephritis, platelet disorders and hearing loss correspond to Epstein syndrome. The differential diagnosis and inheritance are discussed.

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PROSPECTIVE THERAPEUTICAL TRIAL OF MESANGIOPROLIFERATIVE GLOMERULONEPHRITIS IN CHILDREN

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Mesangioproliferative glomerulonephritis with nephrotic syndrome has been the object of prospective randomized therapeutic trial. Total number of children was 28.Group. A-14 children had been treated with the combination of prednisolone (1 mg/kg body weight/day), cyclophosphamide (2 mg/kg body weight/day), dipyridamole (10 mg/kg body weight(day). Group B-14 children had beed treated by prednisolone and supportive measures only.
The mean age of group A was 8 years 2 moths (2/4-12/7) (y/m) with a mean follow up period of 6 years and 6 month (1/0-15/6). The mean age of group B was 6 years 11 months (1/2-13/3), with a mean follow up of 5 years 6 months (1/10 -13/0.). The Life Table graphs have been constructed for both groups (A,B), by the use of Logrank Test (Peto,Pike et al.). Chi square test confirmed the difference in life expectation between the two groups 0,025) P) 0,01.

CONCLUSIONS: The natural course of mesangioproliferetive glomerulonephritis with nephrotic syndrome may be favourable influenced by the combination of prednisolone, cyclophosphamide and dipyridamole.

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COMPLEMENT (C) SYSTEM, IMMUNE COMPLEXES (IC) AND PHAGOCYTIC ACTIVITY (PA) IN CHILDREN WITH GLOMERULONEPHRITIS (GN)

V.V.Fokeeva, T.V.Vinogradova, V.I.Karnaukh

Complement components C1q, C3, C4, $C3^{Nef}$ have been examined with radial immunodiffusion assay of Manchini et al. (1978), IC with PEG and latex tests and neutrophil PA with the test of Vinogradova et al. (1986)+ in 171 patients with GN. A proportional decrease in C1q (0.08-0.11 g/l), C3 (0.50-0.6), C4 (0.14-0.18 g/l) and normal $C3^{Nef}$ (0.12-0.15 g/l) levels, i.e. the classical C activation pathway, were seen in 83% of patients with benign clinical progress. Torpid GN was associated with depressed C3 (0.34-0.50 g/l) and increased C1q (0.18-0.22 g/l), C4 (0.32 to 0.40 g/l), $C3^{Nef}$ (0.22-0.24 g/l) levels depicting the alternative C activation pathway. A proportion of children with proliferative mesangial GN (PMGN) showed IC levels which were 1.5-2-fold above normal regardless of C activation patterns. This type of GN was characteristically associated with a decrease in PA (mean, 60-80%) and high IC levels. High IC levels in GN may be related to both excessive synthesis and impaired elimination of IC in the presence of the alternative C activation pathway coexisting with low PA. Reduced PA, especially in GN patients with the classical C activation pathway, may be a factor in abnormal elimination and persistence of IC, contributing to chronic and prognostically poor course of PMGN. These findings suggest a need for evaluation of various aspects of IC elimination when high IC levels are found in GN patients.

+T.Vinogradova, M.Kapelko et al. Immunology, 1986, No 5, p 63

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IGA NEPHROPATHY AND CYTOMEGALOVIRUS

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The finding that antibodies against cytomegalovirus (CMV) bind to the glomerular mesangium in patients with IgA Nephropathy (IgAN) leds to the speculation that CMV is involved in the pathogenesis of IgAN.

To verify this hypothesis we have invesigated the presence of CMV in 15 patients with primary IgAN,10 patients with other forms of glomerulonephritis (GN) free of immunodepressive drugs and 10 age-matched controls. CMV has been detected in the urinary cells and circulating white blood cells by two different techniques: a)indirect immunofluorescence using monoclonal antibodies specific for CMV antigens; b)DNA probe based assay complementary to the CMV DNA (after addition and hybridization of the specific DNA probe,CMV has been detected enzimatically). IgG and IgM antibody serum levels against CMV has been evaluated by Elisa technique in all groups.

By means of both employed techniques CMV has been detected, as in the urinary cells as in the circulating white blood cells,in almost all IgAN patients and,similarly,in the "other GN" group and the control group. There has been no significant difference in the proportion of seropositive or in the serum CMV IgG antibody levels between the groups. Detection of CMV IgM antibodies has been negative in all subjects.

Our findings do not support the hypothesis that CMV is specifically related to IgAN or is involved in the pathogenesis of IgAN.

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TOTAL LIPODYSTROPHY (TLD) ASSOCIATED WITH NEPHROPATHY AND CLINICAL FINDINGS OF CONNECTIVE TISSUE DISORDERS (CTD)

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Partial Lipodystrophy (PLD) is associated with type II membranoproliferative glomerulonephritis(MPGN). To our knowledge TLD was associated to MPGN II only in one adult. 3 cases of systemic lupus erythematosus associated with PLD have been described in the literature. CASE REPORT. Male, birth weight 3920 gr, unremarkable family history; failure to thrive and 3 episodes of fever with maculopapular lesions after the first month of life; renal and hepatic failure was diagnosed in the 6th month of life (negative TORCH and HBsAg) .At 10 months of age, the patient was first admitted to our Division in serious condition: fever, hypertension, maculo-papular lesions on the face, neck and limbs were noted; creatinine clearance 36ml/m²/1.73sqm, increased SGOT and SGPT , all CTD serologic investigations were normal;furthermore, the absence of subcutaneous fat on the limbs, muscular hypertrophy and hepatomegaly suggested TLD. Renal biopsy: L.M. : membranoproliferative glomerulonephitis type I; E.M.:subendothelial electron-dense deposits in some glomeruli and mesangial cells proliferation in others, viral-like particles in the endothelial cells. I.F.: IgG ++,IgA +, IgM +, C3 ++, k chains ++, lambda chains ++, granular and segmental fluorescence involving almost all glomeruli.The possibility of CTD was hypothesized and Methylprednisolone pulse therapy was initiated, followed by Prednisone; after this treatment improvement of general condition and cutaneous lesions, disappearance of the fever were noted. Follow-up: during the first 8 months of steroid therapy 3 relapses occurred (fever, cutaneous lesions and worsening of renal failure), associated with a shift in therapy to every other day (first relapse occurred during combined Prednisone-Cyclophosphamide treatment). Azathioprine was added in the 8th month of steroid therapy. Cutaneous lesions evolved to erythema multiforme and, recently, face, neck and hands showed hyperkeratosis and hyperpigmentation. At the last examination (age 3 yrs and 7 months): weight -2DS, length -3DS, unmodified TLD, hypertension ; creatinine clearance 50 ml/m²/1.73sqm, serologic investigation of CTD still negative,presence of microscopic hematuria and proteinuria (<0.6 g/24h). Main peculiarities of this case are : 1) the association of TLD and MPGN type I with CTD clinical picture suggestive; 2) in spite of negative serologic investigation, steroid therapy response, apparent corticodependence and the absence of the progression of the disease with Azathioprine suggests a diagnosis of CTD, The association of TLD and MPGN II with CTD, which has already been described only in PLD, could support the hypothesis that PLD and TLD are not completely distinct.

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CLİNİCAL EFFECTS OF PULSE THERAPY İN MEMBRANOPROLİFERATİVE GLOMERULONEPHRİTİS TYPE I AND RAPİDLY PROGRESİVE GLOMERULONEPHRİTİS.

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Membranoproliferative glomerulonephritis (MPGN) has been thought to have a relatively poor prognosis with slowly progressive course. The presence of crecents in MPGN indicates o poor outcome. Rapidly progressive glomerulonephritis (RPGN) outlook becomes as number of of glomeruli affected by crescents increases.

The aim of the present report was to study the effect of combined therapy of pulse therapy and oral prednisone in the MPGN type 1 and RPGN patients with idiopatic glomerulonephritis.

A total of patients, 4 girls and 6 boys with diffuse proliferative MPGN were followed over 2–5 years. 10 children, 7 boys, 3 girls with RPGN were followed for 3–12 years. Total of 20 patients were treated with pulsed methyl prednisolone therapy (1gr/1.73M²) prednisone (2 mg/kg than decrease dosage during 8 months in average) 2 cases with MPGN were treated with oral prednisone with cyclophosphamid.

Hematüria is absent in 6 of 10 patients, 4 have no proteinüria and 8 are normocomplementemic with MPGN type I, No one is azotemic a hypertansive. Repeat renal biopsy were performed at the end of the regimen in the all cases mesangial hypersellularity and cresents decreased. 8 of 10 patients with RPGN showed improvement in renal function 2 months after tretment. During this observation only 2 patients with RPGN developed end stage renal disease 2 years after the onset and one patient died during the dialysis. The other one entered hemodialysis–transplantation programme. We performed biopsy in 8 cases after intensive therapeutic regimen, in all cases percentage of crescents decreased.

From these data this therapy is conceived in management of MPGN typeI and RPGN with idiopatic glomerulonephritis. This therapeutic regimen improves renal function.

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PLASMAPHERESIS IN CHILDREN WITH HAEMOLYTIC URAEMIC SYNDROME (HUS) OLDER THAN FIVE.

Italian HUS Collaborating Group and International HUS Registry.
Presented by A.Gianviti, Bambino Gesù Children's Hospital, Institute for Scientific Research, Roma-Italy.

It is known that plasmapheresis (PF) improved the prognosis of thrombotic thrombocytopenic purpura in adults and that the prognosis of HUS is worse in older children than in infants. Data available on the use of PF in children with HUS are very scanty and were not usually obtained from a selected population of patients at high risk for poor prognosis. The aim of this study was to report on nine children with HUS older than 5 and with a very low prognostic score, who were treated with PF.

Material and Methods: 9 children (5 m, 4 f, age 5y 3m to 14y, mean: 9y), underwent therapeutic PF (2-7 exchanges, mean:4.3). The following three prognostic factors were considered: a)age at onset > 5y, b) the occurrence of the disease in May-September and c) the presence of diarrhoea in the prodromic phase; (best prognostic score (PS) = 3,worse = 0).

Results: the average PS was: 0.66 (range 0-2) and was 0 in four. All children presented acute renal failure and serum creatinine at admission was 1-10 mg% (mean:4.7mg%). Follow-up was 1 y in 8 and 3 mos in 1. At the end of known follow-up all children were alive. Serum creatinine was between 0.4-1.1 mg% (mean: 0.7 mg%) and creatinine clearance between: 50-140 ml/min/1.73 sqm (mean: 95 ml/min/1.73sqm). 7 patients (78%) recovered renal function completely but one has mild hypertension; in 2 (22%) GFR was 50-70 ml/min/1.73 sqm. B.P was normal in 7/9 patients. Minimal urinary abnormalities were present in three children. Therefore complete recovery was obtained in 6 (67%).We also considered the outcome of 22 patients with HUS older than 5, with average PS 1.2 (range 0-2) not treated with PF. 59% had normal renal function after 1 year follow-up and 41% were in chronic renal failure.

Conclusion: data presented here on children with HUS older than 5 and with a very low PS confirm that a bad renal prognosis is to be expected in 33-41% of the cases. The different results of this retrospective study with and without PF do not allow us to draw conclusions about the possible usefulness of this procedure. A multicenter randomized trial is warranted.Supported by CNR Grant:89.046.73.

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USE OF URINARY PROTEIN/CREATININE RATIOS IN THE FOLLOW-UP OF PATIENTS WITH HAEMOLYTIC URAEMIC SYNDROME.

DV Milford, P Barry, RHR White, CM Taylor.

Four children who recovered from diarrhoea-associated (D+) haemolytic uraemic syndrome (HUS) had an initial period of stable renal function with a subsequent decline in GFR 10 or more years from diagnosis. In all cases a rise in proteinuria preceded decline in renal function. We have previously validated early morning urine (EMU) protein/creatinine ratios (Up/Uc) for quantifying protein excretion [1], the upper limit of normal being 20 mg/mmol.

We have since used EMU Up/Uc prospectively in the follow-up of 40 HUS patients to determine whether this is a useful monitoring technique. All patients considered to have a poor outcome (defined as one or more of the following: hypertension, height/creatinine < 1.5 or ESRF) had markedly abnormal Up/Uc at one year's follow-up. By contrast all patients with normal values at one year had recovered fully ($p<0.001$, Mann Whitney). The rate of decline in proteinuria was significantly different between good and poor outcome groups.

These data support the use of EMU Up/Uc in HUS follow-up, and have enabled us to formulate an algorithm to optimise the management of these patients.

[1] Simplified quantification of urinary protein excretion in children. J S Elises, P D Griffiths, M D Hocking, C M Taylor, R H R White. Clinical Nephrology 1988; 30:225-229.

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RENAL FUNCTIONAL RESERVE IN CHILDREN FOLLOWING RENAL TRANSPLANTATION (TX).

U.Berg and M. Englund

During the last years great interest has been focused on the renal reserve capacity specially in patients with reduced renal mass. The aim of the present investigation was to study renal reserve capacity in children following renal tx and compare it with other patients with solitary kidneys.
21 children, 1.4 -15.4 (median 7.2) years at tx were investigated 0.3 - 5.7 (median 1.5) years post-tx. All patients were treated with Cyclosporine (CsA), 7 patients in combination with low dose prednisolone and 14 were given triple therapy including azathioprine. Renal function was investigated as GFR and ERPF determined by clearances of inulin and PAH according to standard clerance technique during water diuresis. After three 30 min urine collection periods a protein rich meal containing 1.5 g protein/kg body weight was given and urine was collected for another three hours. The response to the protein meal was calculated as the mean value of the six 30 min collection periods after the meal. 9 children, 7.1 - 16.0 years, with solitary kidneys because of renal agenesis or following nephrectomy and 4 adult parent donors served as controls.
Results: Mean GFR and ERPF of the tx children before the protein meal was 63±21 and 323±88 ml/min/1.73 sq.m. resp. and increased significantly following the protein rich meal to 66±18 and 350±86 ml/min/1.73 sq.m. The 9 children with solitary kidneys increased their GFR from 97±12 to 103 ± 18 ml/min/1.73 sq.m. while ERPF did not show any significant change. The four donors increased their GFR and ERPF from 74±8 and 327±23 to 84±13 and 368±36 ml/min/1.73 sq.m. respectively.
Conclusion: Renal reserve capacity is well preserved in children following renal transplantation as well as in other children with solitary kidneys.

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FUNCTIONAL RESERVE OF THE REMNANT KIDNEY : A LONG-TERM STUDY IN PATIENTS UNINEPHRECTOMIZED DURING CHILHOOD

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Unilateral nephrectomy is associated with hyperfiltration in the remnant kidney, a phenomenon that could ultimately damage the remaining nephrons and diminish their functional reserve. To test this hypothesis, the renal response to acute protein loading (1 g/kg, orally) was studied in 37 patients uninephrectomized during childhood. Seven patients had been nephrectomized less than 5 years before the study, and 13 more than 20 years (max. 29.1) before. Indications for nephrectomy were : multikystic dysplasia, ureteral stenosis and severe renal scarring. A control group of 7 healthy volunteers matched for age with the latter group was studied in similar conditions. Creatinine clearance, measured on alternate years, had remained stable in all the patients throughout the follow-up period.

Results : The increase in GFR (C_{inulin}) following protein loading - the so-called functional reserve - was identical in the recently nephrectomized patients and in the control group (+27 ± 7 and +26 ± 14 %), the increase in the filtration fraction being greater in the recently nephrectomized patients. The functional reserve tended to decline 10 years after uninephrectomy. In the 13 patients nephrectomized more than 20 years before the study, the increase in GFR was significantly reduced (+6.4 ± 2 %) when compared to controls ($p<0.025$), while basal GFR and RPF (C_{PAH}) were similar in both groups. These results demonstrate a delayed decrease in the functional reserve on the remnant kidney, which may only be noticed more than 20 years after uninephrectomy.

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HYPERFILTRATION IN PATIENTS WITH GLYCOGEN STORAGE DISEASE TYPE I (GSD I)

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Renal failure has been reported recently as a late complication of GSD I. This is presumably due to glomerular hyperfiltration which progresses to focal glomerulosclerosis. Additional to GFR, which has been already measured by other authors, we measured RPF in 23 patients with GSD I (mean age 10.9 years, range 2.2-21.6 years).

	GFR[a]	RPF[b]	FF
patients	188 ± 50	927 ± 292	0.21 ± 0.04
normal adults	90 - 145	327 - 679	0.21 - 0.28

a: ^{125}J iothalamate; b: ^{131}J hippurate, both measured by continuous infusion technique; results in ml/min/1.73 m^2.

Hyperfiltration (GFR > 145) was found in 18/23 patients. The lowest GFR was 98. There was no significant difference for those values in different age groups. At follow-up of 14 patients after a mean of 2.5 years (1-7.5) GFR and RPF did not significantly change despite the fact that three of them (all older than 15 yr) developed persistent glomerular proteinuria (0.1, 0.5 and 0.9 g/day). Renal length (related to height), measured by ultrasound in 21 cases, was positively correlated to GFR and RPF. Tubular function (glucosuria, beta-2-microglobuline- and lysozyme excretion,and TRP) was normal in all patients.
We conclude that not only hyperfiltration but also considerable increase in RPF occur as persistent abnormalities in most GSD I patients, progressing to proteinuria in older patients. The relative increment of kidney length appears to be related to the degree of hyperfiltration.

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EFFECT OF AGE AT NEPHRECTOMY ON LONG-TERM CHANGES OF RENAL FUNCTION OF UNILATERALLY NEPHRECTOMIZED RATS.

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We have reported that unilateral nephrectomy (uNx) in rats at the age of 6 weeks eventually results in renal failure. The period of stable GFR and the rate of fall of GFR were affected by dietary protein intake. Proteinuria preceded the decline of GFR. Young and adult rats respond differently to uNx. This may affect the long-term outcome.

We have compared long-term effects of uNx at the age of 3 (uNx3) with 15 weeks (uNx15) in rats fed 12% (LP), 24% (NP), or 36% (HP) protein diets. Groups initially consisted of 15 rats. Every 12 weeks, the GFR (plasma clearance of ^{51}Cr-EDTA) and urinary protein excretion (Coomassie blue) were assessed.

The GFR of rats on different dietary protein intake and the same age at time of uNx were significantly different. No differences between GFR in uNx3 vs uNx15 were found. However, uNx3 rats on an HP diet initially had significantly higher proteinuria than uNx15 rats. The uNx3 rats on an LP or NP diet had significantly higher proteinuria at 24 and 36 weeks post-uNx. Comparing the period of stable GFR of uNx3 and uNx15 rats, indicated that the lengths of these periods were significantly shorter in uNx3 rats (63 ± 18 vs 77 ± 20(wks) on LP, 33 ± 12 vs 45 ± 22(wks) on NP, 24 ± 14 vs 39 ± 12(wks) on HP). Significant effects of protein intake on the length of stable periods were present. No significant differences in the rate of fall of GFR between uNx3 and uNx15 rats were present (-0.17 ± 0.08 n = 10 vs -0.19 ± 0.08 n = 5 (ml/min*12 wks) on NP, -0.35 ± 0.15 n = 13 vs -0.37 ± 0.08 n = 5 (ml/min*12 wks) on HP; uNx3 vs uNx15). On LP diet not enough rats with a fall of GFR were available to determine the rate of fall. The rate of fall of GFR on HP diet was significantly higher than on NP diet.

We conclude that uNx3 and a high protein intake negatively affects the length of the period of stable GFR post-uNx. A high protein intake, but not the age at uNx, negatively affects the rate of fall of GFR.

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EFFECT OF VARIOUS ANTI-HYPERTENSIVE DRUGS ON RENAL LESIONS AFTER SUBTOTAL NEPHRECTOMY (Nx) IN RATS UNDER TWO SODIUM DIETS.

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The beneficial effect of angiotensin converting enzyme inhibitors (ACEI) on renal deterioration has been claimed, but most studies used a Nx model causing hypertension, and very few compared the effects of other drugs. Our aim was : 1) to use a model with little hypertension, 2) to compare the effects of enalapril (E : 3 mg/kg/day) to those of other drugs : cicletanine (C : 4 mg/kg/d) and guanfacine (G : 5 mg/kg/d) and of placebo (P). Drugs were given by daily gavage in normal (n = 8 per group) and uremic (n = 12-17 per group) rats. **Study I** used a standard chow (20% protein ; 0.5% Na) and compared E, C and P. In **Study II** diet Na content was reduced to 0.2%.

In **normal rats** blood pressure (BP) was similar in both studies and was slightly reduced by E (105 mmHg vs 125 mmHg in the other groups).

In **study I** uremic rats rapidly developed hypertension (P : 141, 146 and 160 mmHg at 3, 6 and 9 weeks (w)) which was unaffected by C (139, 130 and 148 mmHg) and E (133, 148 and 176 mmHg, despite ACE inhibition). They had a high mortality rate with a similar rise in proteinuria and in plasma creatinine levels. At sacrifice (12 w) renal lesions did not differ in P, C and E groups (5/12, 7/14 and 10/16 rats with ≥ 25% sclerosed glomeruli).

In **study II** the decreased Na intake did not affect weight gain of any rat group. In uremic rats it resulted in lower hypertension (P : 131, 138, 149 mmHg at 6, 12, 24 w), which was well controlled by E, C and G. The control was better with E (102, 103, 110 mmHg at w 6, 12, 24) than with C (118, 125, 131 mmHg) and with G (110, 122, 124 mmHg) (E vs G, C p<0,001 ; G, C vs P p<0,005). Drugs did not change diuresis, and Na excretion. At sacrifice (24 w) proteinuria was : 66±24 in E (p<0,02 vs P) , 89.7±24 in G (p<0,05 vs P), 170±34 in C and 188±46 mg/24 h in P rats ; the percent of sclerosed glomeruli differed (p<0.002) and was ≤ 10% in 3/10 P, in 3/11 C (ns vs P), in 14/15 E (p<0.002 vs P) and in 10/13 G (p<0.03 vs P).

In **conclusion** : despite a good control of BP, the beneficial effects of the 3 antihypertensive drugs on remnant kidney function and deterioration differed : they were dramatic with ACEI, good with G and absent with C. A moderately Na restricted diet is necessary, in this model, for restoring the action of antihypertensive drugs. It also reduced hypertension and slowed the renal deterioration rate.

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MULTICENTER RANDOMIZED STUDY ON THE EFFECT OF A LOW PROTEIN DIET ON THE PROGRESSION OF CRF IN CHILDREN - ONE YEAR RESULTS

A.-M.Wingen, C.Fabian for the European Study Group for Nutritional Treatment of Chronic Renal Failure in Childhood

(BMFT grant 07047420, O. Mehls)

In CRF a high protein intake may induce glomerular hyperfiltration and damage of renal parenchyma. The aim of this multicenter study is to investigate the effect of a low protein intake amounting to the WHO safe levels (1.1-0.8 g/kg/day) on the progression of renal failure and on growth of the patients. 212 patients from 24 centers (148 male, 64 female; median age: 9.9 years range: 2-18 years) have been included into the study. 108 patients have passed the six-months run-in period and the first year after stratification according to the underlying renal disease and randomization for protein intake. No significant influence of the dietary regimen has been noted so far. Mean GFR at start of study was 36 ± 15 ml/min/1.73m^2 (calculated after Schwartz). The mean loss of GFR per month was 0.21 ± 0.49 ml in the low protein group and 0.21 ± 0.5 ml in the control group. A mean loss of GFR of 0.27 ml/month in patients with glomerular diseases and 0.15 ml/months in patients with hypoplastic kidneys and uropathies may point to differences related to the renal disease, but, no significant dietary effect was seen within a subgroup. Body growth was not negatively influenced by the low protein diet. Mean SDS for height velocity was +0.2 ± 1.6 in the low protein group and -0.02 ± 1.5 in the control group.

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MULTICENTER PROSPECTIVE RANDOMIZED STUDY ON THE EFFECT OF PROTEIN RESTRICTION ON RENAL FUNCTION AND GROWTH OF CHILDREN WITH CHRONIC RENAL FAILURE.

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Although a protein restricted diet is frequently used in chronic renal failure it is as yet not proven whether it has a beneficial effect on renal function of children with chronic renal failure. We wanted to know if a protein restricted diet can slow down or even prevent progression of chronic renal failure and whether growth of these children would be affected. 56 children with chronic renal failure (GFR 18-63 ml/min/1.73 m², mean 39 ml/min/1.73m²) entered the study. Age: 2 - 17 yrs, mean 9 yrs and 4 months. Sex: 41 boys and 15 girls. Diagnosis: glomerulopathy (9); reflux nephropathy, obstructive uropathy and/or dysplasia (36), miscellaneous (11). All children are seen once every three months by the same pediatrician and dietician. After an observation period of three months the children were randomized in a group with a protein restricted diet (safe levels WHO 1985: 0.8 - 1.1 g/kg/day, dependant on the age of the child) and a control group with a protein intake of at least 1.5 - 2.0 x safe levels WHO. Results after a follow up period of two yrs.: GFR does not differ significantly between the protein restricted and the control group. Growth expressed as delta height standard deviation was equal in both groups. Protein intake calculated from three day prospective dietary diaries indicated a good dietary compliance for most children in the protein restricted group. Blood urea and blood urea/creatinine ratio were significantly lower for the protein restricted group compared to the control group. Supported by the Dutch Kidney Foundation, grant no. C 87.648 and part of the European multicenter study, BMFT grant no. 07047420/FRG.

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SEROLOGICAL FEATURES AND VEROTOXIN ASSOCIATION OF THE PROTOTYPIC HEMOLYTIC UREMIC SYNDROME (HUS)

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Prototypic HUS has been related to preceding intestinal infections by Verotoxin (VT) producing Escherichia coli (VTEC) O157:H7 and other serovars. Micropathic hemolytic anemia and acute nephropathy have been postulated to be toxin-mediated following direct damage of the renovascular endothelium. However, the frequency of reported VT assocation varies depending on demographic factors and technical reasons.

In a 4-years prospective study on HUS at Hamburg, Northern Germany (n=22 pts; median age 2;2 yrs), VT-association was examined by HeLa-cell assay for free fecal VT (FVT), coproculture and colony-blot-hybridization with VT-specific DNA probes. Serial serum samples of 12 pts were studied for VT neutralizing antibodies (NAb) using toxin preparations from defined E.coli strains and for hemagglutinating antibodies using erythrocytes coated with purified LPS (indirect hemagglutination) from E.coli O157:H7 and other serovars as controls (LPS-Ab).

VT was detected in 13/22 children (59 %); VTEC isolates (n=6) included serogroups O26, O55, O111 and O157; FVT alone was found in 7 cases. 4/12 pts developed rising NAb-titers against VT1 and/or VT2; 9/12 pts (75 %) had elevated Ab against LPS-O157 at the time of the diagnosis of HUS but not against other O-antigens. Clinical variables and outcome did not differ in respect to the presence of VT and/or elevated neutralizing or LPS-O157 specific Ab.

Thus LPS-O157-Ab appear to be an early and new valuable serological marker to identify and characterize further cases of protypic HUS. The pathogenic or protective role of VT- and LPS-specific Ab needs further elucidation.

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THE ROLE OF THE FIBRINOLYTIC SYSTEM IN THE EPIDEMIC FORM OF HEMOLYTIC UREMIC SYNDROME.

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In the human fibrinolytic system plasminogen is activated to plasmin by the action of several activators, the most important being tissue-type plasminogen activator. The activation of plasminogen is also regulated by a specific plasminogen activator inhibitor. Plasminogen-activator activity (PA) and plasminogen activator inhibitor activity (PAI), both originating from endothelial cells, were measured in plasma of ten children with hemolytic-uremic syndrome (H.U.S.) before and after stimulation by DDAVP infusion. In the acute phase a lowered or absent baseline PA was demonstrated in ten out of ten patients. The PAI was increased in 4/10. In these four patients PA could not be stimulated by DDAVP. In 5 out of 6 with normal PAI, PA was increased after DDAVP.

Two to three weeks after the acute phase the same investigation was repeated and normal values were obtained in all patients. It is conceivable that the temporary defect in the fibrin-clearing system contributes to the persistence of thrombi in the microvascular system of children with H.U.S.

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PREDICTION OF EXTRA-RENAL COMPLICATIONS AND RENAL OUTCOME IN HAEMOLYTIC URAEMIC SYNDROME.

Kevin P Morris & Malcolm G Coulthard.

Since 1970 we have seen 105 children with diarrhoea-associated haemolytic uraemic syndrome (HUS). Only 6 cases were rhesus negative ; significantly lower than expected ($p<0.05$). Moreover this group were more likely to develop extrarenal complications ($p=0.02$) and early death ($p<0.02$).

A significant increase in incidence from 1982 and a change in clinical features pre/post 1982 including the age at presentation (mean 32.7 v 54.0 months;$p=0.002$) and the neutrophil count at presentation ($p<0.03$) suggest a possible alteration in the disease around that time. Further analysis was therefore confined to the 78 cases since 1982.

Poor renal outcome was seen in 7 (11%) of the 64 with an adequate follow up period. 4 have hypertension. 1 was transplanted, 4 have chronic renal failure and 1 other has proteinuria.The use of FFP in 41% of cases did not reduce the incidence of renal sequelae or extra-renal involvement. We applied our data to a scoring system that was designed to predict poor renal outcome (Birmingham group, BPA, 1988). We found it to be a poor predictor of renal outcome (sensitivity 33%, specificity 83%). We found a relationship between poor renal outcome and presentation in the spring ($p=0.02$), the WBC count at presentation ($p<0.05$) and the duration of anuria ($p<0.0001$); anuria in excess of 10 days predicted poor outcome with a sensitivity of 86% and a specificity of 91%.

Severe extra-renal involvement occurred in 13 of the 78 children (17%) with multiple seizures (7), coma (4), hemiparesis (2), necrotising enterocolitis requiring bowel resection (4), diabetes mellitus (2) and oesophageal stricture (1). Two of this group died of acute cerebral disease. There was no correlation between the presence of extra-renal disease and subsequent renal outcome; 8 of the 11 survivors have no renal sequelae. The Birmingham score infact predicted severe extra-renal disease ($p<0.003$) better than poor renal outcome. Other associated parameters were the trough platelet count, the plasma sodium at presentation and the duration of anuria.

Outcome predictors. In our HUS cohort the Birmingham score predicted extra-renal disease but anuria longer than 10 days was a much better predictor of poor renal outcome than any scoring system currently available.

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HEPARAN SULFATE PROTEOGLYCAN (HSPG) CONTENT OF GLOMERULAR BASEMENT MEMBRANE (GBM) IN THE CONGENITAL NEPHROTIC SYNDROME (CNS) OF THE FINNISH TYPE

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CNS is an unusually fatal disorder in which heavy proteinuria and the nephrotic syndrome are present from birth or early infancy. The main subgroups are the Finnish type (CNF) and diffuse mesangial sclerosis (DMS). A decreased concentration of HSPG in the GBM is supposed to be responsible for the increased glomerular permeability in CNS. We analysed the glycosaminoglycan (GAG) content of the GBM from 3 CNF and 16 control infants. Comparison of the GAG content of GBM from CNF patients and controls did not reveal significant differences. Also the GAG composition was comparable and HS constituted at least 75% of the GAG content. Immunofluorescence studies of normal human infant kidney tissue with monoclonal or polyclonal antibodies (against the core of protein of human GBM HSPG) showed a linear staining of almost all renal basement membranes. Kidney tissue from 3 CNF patients did not show discernible differences in the distribution of quality of the staining. In addition we observed, however, an intense reaction for HSPG in the glomerular mesangium in the 3 CNF patients. These results are in contrast to the decrease of anionic sites (PEI staining) and the replacement of GBM HS by chondroitin sulfate, observed by others.

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GLOMERULAR BASEMENT MEMBRANE IN CONGENITAL NEPHROSIS OF THE FINNISH TYPE (CNF)

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The pathogenesis of congenital nephrosis is not known. The prevailing theory suggests, that a loss of anionic charge in glomerular basement membrane (GBM) caused by a decrease in heparan sulphate proteoglycan (HSPG), is responsible for the protein leakage. CNF is congenital disease with a massive proteinuria starting at birth. As a genetic disease, it serves as an excellent model for studies on nephrosis.

Ex-vivo perfusion of the nephrectomized kidneys with a cationic label, polyethyleneimine, did not show a difference in the amount of anionic sites in lamina rara externa in CNF (38-45 sites /1000 nm) as compared with normal infant or adult kidneys (28-46 sites/1000 nm). In vitro staining of the kidney tissue with cationized ferritin and ruthenium red also gave similar patterns. Total glycosaminoglycan and HSPG contents in isolated GBM from CNF and control kidneys were equal. The expression of other components of the glomerular filtration barrier (type IV collagen, laminin, fibronectin, podocalyxin) were studied by immunofluorescence. The staining patterns were normal in CNF.

The results indicate, that proteinuria in CNF is not due to a loss of anionic charge or any major components of GBM.

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LEVAMISOLE IN CORTICOSTEROID DEPENDENT NEPHROTIC SYNDROME: A DOUBLE BLIND, PLACEBO CONTROLLED TRIAL

T J Beattie (On behalf of the British Association for Paediatric Nephrology Research Group)

To date the efficacy of Levamisole (Lev) in corticosteroid responsive nephrotic syndrome has been evaluated only on an uncontrolled basis. Despite these limitations the results suggest some benefit. The purpose of this study was to assess the benefit/toxicity ratio of Lev in patients with nephrotic syndome of presumed or proven minimal change histology, who remained dependent on significant doses of Prednisolone (P), using a multicentre, randomised, double blind, placebo controlled, parellel group study.
Patients known to be P sensitive and dependent on a dose of $\geq$ 0.5mg/kg on alternate days, irrespective of prior alkylating therapy were recruited. Following a P induced remission, these patient categories were randomised to receive either Lev at 2.5mg/kg on alternate days or placebo (C). Following entry, P was progressively reduced and stopped by 56 days. Lev or C was continued for a maximum of 112 days.
The main outcome indicator was time between entry and confirmation of the first relapse. If relapse occured before 112 days the patient exited from the trial.
56 patients (28 Lev, 28 C) have completed the trial protocol. 18 patients in the Lev group and 16 patients in the C group had received prior alkylating therapy. At 112 days following entry, 12 patients in the Lev group and 5 in the C group remained in remission ($0.1 > p > 0.05$). Of those patients who relapsed before completion of the trial period, the mean time to relapse in the Lev group was 48 $\pm$ 34 days (M $\pm$ SD) and in the C group 44 $\pm$ 29 days (N.S.).

This study suggests that Levamisole may be of some limited value as a "steroid sparing" agent in corticosteroid sensitive nephrotic syndrome.

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STEROID RESISTANT IDIOPATHIC NEPHROTIC SYNDROME AND CICLOSPORINE.

P. Niaudet and the French Club of Pediatric Nephrology.

Steroid resistant idiopathic nephrotic syndrome carries a poor prognosis since about half of the patients progress to end stage renal disease. We report our experience on the effects of ciclosporine in association with prednisone in 31 children with idiopathic nephrotic syndrome. All patients (pts), 13 girls and 18 boys, aged 1 month to 14.3 years at onset of nephrotic syndrome, had failed to respond to daily prednisone 60 mg/m2 for one month followed by three methylprednisolone pulses 1 g/1,73 m2. Four pts had in addition received chlorambucil without beneficial effect. Renal biopsy had shown minimal change disease (MCD) in 19 cases and focal and segmental glomerulosclerosis (FSGS) in 12 cases. Children who had a creatinine clearance less than 50 ml/mn/1,73 m2 or who had had the disease for more than two years were excluded from the study. Ciclosporine, 150-200 mg/m2, was given in combination with daily prednisone, 30 mg/m2, for 1 month and with alternate day prednisone, 30 mg/m2, thereafter for 5 months.
Fourteen pts went into complete remission, 9 of them during the first two months of therapy. Three patients had a partial remission. The remaining 14 pts failed to respond to the treatment. The response to ciclosporine and prednisone was not correlated to the histopathological findings since, among the 14 pts who responded to the treatment, 9 had MCD and 5 FSGS whereas, among the 14 pts who failed to respond to the treatment, 9 had MCD and 5 FSGS. Among the side effects of the treatment, one patient with FSGS progressed rapidly to end stage renal failure after 2 months of treatment. The responsability of ciclosporine, although not proven, may be suspected. Ciclosporine was withdrawn in another patient because of a reduction in creatinine clearance which returned to normal values afterwards. High blood pressure was observed in 12 pts, hypertrichosis in 18, gum hypertrophy in 11, vomitings or diarrhea in 2, headaches in 1 and gynecomastia in 1. These preliminary data suggest that ciclosporine in combination with prednisone may be efficient in patients with steroid resistant nephrotic syndrome with either MCD or FSGS.

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A MULTICENTER RANDOMIZED STUDY OF CYCLOSPORIN A COMPARED WITH CYCLOPHOSPHAMIDE IN STEROID-DEPENDENT/FREQUENTLY RELAPSING NEPHROTIC SYNDROME: EVALUATION OF TREATMENT EFFICACY. A Edefonti, L Ghio, G.Rizzoni, R Gusmano, G Lama, G Zacchello, A Andreucci, A Castellani, G Cinotti, R Confalonieri, A Bettinelli, A Perini, S Rinaldi, O Della Casa, C Ponticelli.

Steroid dependent/frequently relapsing nephrotic syndrome (SD/FR NS) still represents a major clinical problem, due to the severe side-effects of longterm steroid treatment. Cyclophosphamide (CF) is considered a valuable tool in order to reduce the number of relapses and modify the course of the disease. Controlled studies about Cyclosporin A (CSA) efficacy in SD/FR NS are in the other side still lacking. At this purpose a multicenter prospective randomized study comparing CSA and CF in SD/FR NS was designed. Duration of CSA treatment was 9 months, at 6 mg/kg/day, initial dose, plus 3 months at tapered doses. CF, 2,5 mg/kg/day, was administered for 2 months. Prednisone (PN) was given to induce remission of NS, then tapered after the onset of either drug and withdrawn after 8 weeks. Relapses were treated with PN, according to ISKDC. Two 1 year periods, before (basal period) and following randomization (treatment period) are considered for this study. Fifty five chidren, 30 assigned to CSA, 25 to CF, comparable for age at first diagnosis, present age and number of relapses during the basal period, entered the study. Percentage of complete remission (%CR), number of relapses/patient/year (N rel/pt/yr) and total dose of prednisone (mg/kgBW) were calculated in the 2 periods in each treatment group. Data of CSA group were then compared with CF group. Results:

	%CR	N rel/pt/yr BASAL/TREATMENT	PN (mg/kg) BASAL/TREATMENT	
CSA	100	5±0.5 * 2.5±0.3	171±127 * 93±281	
CF	100	48±0.4 * 2±0.2	211±111 * 38±31	* $p \leq 0.01$

No significant difference was found between CSA and CF treated groups as far as these parameters are concerned. In conclusion both CSA and CF resulted in a decrease of the frequency of relapses and the amount of corticosteroids administered in the first year after randomization. Data concerning the following year are still in progress.

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SENDAI VIRUS INDUCED IgA NEPHROPATHY IN MICE

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Upper respiratory tract viral infections are one of the most common events eliciting macroscopic hematuria in IgA nephropathy. Sendai respiratory virus has been demonstrated to be able of inducing IgA immune deposits in mice. Aim of this work was to gain further insight into the mechanisms governing IgA immune deposition and the related urinary abnormalities in mice immunized with this virus.

Forthy (C57BC/6 x DBA/2)F1 adult male mice, maintained in separate rooms isolated from the other animals were studied by different protocols. G1 (5 mice) were immunized subcutaneously with cholera toxin-conjugated Sendai virus, egg-passaged. G2 (9 mice) were twice subcutaneously immunized with ß-propiolacton inactivated Sendai virus. G3 (6 mice) were twice intranasally immunized with inactivated Sendai virus and then intranasally injected with alive Sendai virus. G4 (10 mice) were intranasally immunized five times with inactivated Sendai viruses. G5 (10 mice) were the control group. After 40 days blood was collected for test before the i.v. challenge with 0.25 mg of alive Sendai. The day after, blood, 24 hour urine and kidney tissue were analyzed.

IgA bright mesangial deposits and granular C3 deposits were evident in 50-100% and 50-70% respectively of G1-G4 mice but only in 0-10% of G5 mice.Sendai antigen was detectable in 33-40% of G1-G4. No difference was demonstrated by scoring IF positivities. The 4 groups differed for IgG deposition which was most evident, almost prevalent over IgA in G1 ($p<0.005$) and G2 ($p<0.005$) vs G3 and G4. Serum IgA antibodies to Sendai virus were significantly increased in G3 and G4 not only vs G5 but also vs G1 ($p<0.0003$) and G2 ($p<0.0001$). Conversely IgG specific response was similar in G1 to G4. All groups had hematuria and proteinuria significantly increased vs G5 ($p<0.0001$), but G1 and G2 had significantly higher values than G3 and G4 ($p<0.001$).

These data indicate that Sendai virus can induce IgA mesangial deposits and the way of sistemic exposure to viral antigens may be chritical for the immunopathological response, since intranasally immunization can induce IgA high antibody response, however proteinuria and hematuria are greater in mice receiving subcutaneous immunization.

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CONTROL OF WATER AND SODIUM BALANCE IN THE PRETERM NEONATE

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Water and sodium balance are important in the clinical management of preterm babies but homeostatic mechanisms are unclear. We therefore studied 24 preterm babies (8 ventilated and 16 non ventilated) of 26 to 35 weeks gestation, in whom glomerular filtration rate and urine flow were measured by continuous Inutest infusion on days 2 to 6. Intakes of fluid (100 or 200 ml/kg/day) and sodium (3 or 6 mmol/kg/day) were controlled using a randomised crossover design in which each baby received a different combination each day over 4 consecutive days. The babies were assessed at the end of each day.

The babies were well during all four regimens, with plasma sodium concentration and blood pressure unchanged and within the normal range. Urine flow was appropriately increased on the high fluid intake days so that water balance was maintained. Similarly sodium excretion was increased on the high sodium intake days thus maintaining a constant mean negative sodium balance of 2.2 mmol/kg/day, regardless of sodium intake. Different fluid and sodium intakes did not alter plasma vasopressin (AVP), which showed a significant relationship to plasma osmolality ($p<0.05$, analysis of covariance), but a stronger relationship to peripheral-central temperature difference ($p<0.01$), a measure which is widely used in older children as an indicator of hypovolaemia. There was no significant relationship between plasma AVP and urinary osmolality.

We conclude that stable preterm babies are able to maintain appropriate sodium and water balance, with ventilated babies apparently having similar control. AVP is released in response to osmotic and non-osmotic stimuli. We suggest that peripheral-central temperature difference may be useful in the monitoring of preterm babies.

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BLUNTING BY WR-2721 OF THE EXPERIMENTAL HYPOXEMIA-INDUCED VASOMOTOR NEPHROPATHY

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In newborn infants, as well as in neonatal and adult animals, severe hypoxemia can lead to renal vasoconstriction and insufficiency. In addition to the immediate effects of O_2 deprivation, a substantial part of renal injury has been ascribed to oxygen free radical generation and calcium accumulation during reoxygenation. A putative protective effect of the organic thiophosphate WR-2721 - a radioprotective agent with hypocalcemic properties - against acute hypoxic renal insufficiency (PaO_2: 35 mmHg) was investigated in 48 young anesthetized rabbits undergoing mechanical ventilation. Five experimental groups were studied: A) control normoxemic rabbits (n=11); B) untreated hypoxic-reoxygenated rabbits (n=13); C) hypoxic-reoxygenated rabbits receiving WR-2721 before hypoxie (n=8); D) hypoxic reoxygenated rabbits receiving WR-2721 before reoxygenation (n=8); E) normoxemic rabbits receiving WR-2721 (n= 8). Glomerular filtration rate (GFR) and renal blood flow (RBF) were assessed by the clearance of inulin and PAH, respectively. The animals of group A showed no changes in renal hemodynamics and function during 150 minutes. In group B, 45-min hypoxemia was associated with a fall in mean blood pressure (MBP), diuresis, GFR and RBF, persisting during 60-min reoxygenation. The same impairment of renal function was observed in the group C during hypoxemia. The intravenous administration of WR-2721 (75 mg/kg b.w.) before hypoxemia (group C) or reoxygenation (group D) prevented the decrease of diuresis and GFR. Filtration fraction increased significantly. The administration of WR-2721 to normoxemic animals (group E) was associated with a decrease in MBP, diuresis and RBF. GFR did not vary. Mean PAH extraction ratio was not modified by WR-2721. Urinary calcium excretion increased while calcemia progressively decreased after the administration of WR-2721. The inability of the hypoxic kidney to recover after a hypoxemic stress could be related to the generation of reactive oxygen free radicals and/or to the increase in intracellular calcium concentration during reoxygenation. The striking improvement in renal function observed in hypoxemic young animals given WR-2721 could be do to the oxygen free radical scavenger and/or hypocalcemic properties of this agent.

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EFFECT OF PHOSPHORUS DIET CONTENT ON RENAL PHOSPHATE AND CALCIUM TRANSPORT CAPACITY IN THE WEANING RAT.

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Renal phosphate transport maturation, which processes through an increase of the carrier affinity for the Na^+-cotransported phosphate, occurs in the rat during the 3rd postnatal week.

The purpose of this study was to examine whether pups were able to adapt their renal Pi transport to the phosphorus content of the diet during the weaning period.

Clearance experiments and brush border membrane studies were performed on 21-day-old rats early weaned on day 16 either on low phosphorus diet (0.19 g %, LPD), normal phosphorus diet (0.78 g %, NPD: control) or high phosphorus diet (1.5 g %, HPD).

In the LPD group, the Pi fractional excretion was lower than in controls (0.3 ± 0.1 % vs 18 ± 3 % respectively, $p< 0.001$). After a perfusion of phosphate (1.5 µmole.min $^{-1}$.100 g^{-1}) it remained very low (0.21 ± 0.05 % in LPD vs 40.5 ± 6.3 % in controls, $p< 0.001$). The Ca fractional excretion in these LPD rats was very high (12.6 ± 1.02 %) compared to controls (0.42 ± 0.2 % $p< 0.001$). In Contrast, HPD rats presented a higher Pi fractional excretion (41 ± 4 %, $p< 0.001$).

Membrane vesicles isolated from 21-day-old rats kept on LPD showed a higher Vmax compared to controls (11466 ± 1840 vs 7019 ± 1112 pmol. mg protein $^{-1}$ .10 s $^{-1}$, $p< 0.01$) and those isolated from HPD rats a lower Vmax (5161 ± 956 vs 7248 ± 1946, $p< 0.01$) . No change in the apparent Km values was observed.

In conclusion: 1) As early as the third postnatal week, the young rat is able to adapt its renal phosphate transport capacity to the phosphorus content of the diet through variations in the number of carrier sites, whithout any change in the carrier affinity. 2) The hypercalciuria observed in the LPD group might be related to the phosphorus depletion, and it must be noted that this latter occured very quickly during this growth period in the rat.

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COMPENSATORY KIDNEY GROWTH(CKG) BY AUTOCRINE IGF II SECRETION IN INFANTILE RATS
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The earlier in life kidney tissue is lost the more pronounced is CKG and the more CKG is characterized by predominance of hyperplasia over hypertrophy(Celsi et al).In adult rats an increased gene expression or increased tissue concentrations of the growth factors IGF I,IGF II,and EGF were observed during CKG.To investigate the specific age dependent pattern of CKG in Sprague-Dawley rats IGF I- and IGF II-serum(SC) and kidney tissue concentrations(KTC) were measured at day 3,5,7 and 10 after unilateral nephrectomy in infantile (IR)and adult rats(AR)(18 vs. 70 days old).
Methods:IGF I was measured by RIA after extraction,IGF II by a specific RRA blocking IGF binding protein by addition of 25 ug IGF I to each tube(Blum et al.).
Results:In AR a significant increase of IGF I-KTC was observed (day5 :x=210,s=125 ;controls: x=138,s=20 ng/g),IGF I-SC increased slightly,IGF I-SC and -KTC were not different from controls.In contrast in IR IGF II-SC(day 5:x=352,s=110 controls:x=226,s=26;day 7:x=267,s=78 controls:x=223,s=23 ng/ml)and IGF II-KTC(day 5:x=141,s=62 controls:x=79,s=18;day 7:x=155,s=23 controls:x=100,s=23 ng/g)were significantly elevated.
These results support the hypothesis that the autocrine secretion of IGF II is involved in CKG by hyperplasia in IR.

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CONTRALATERAL RENAL HYPERTROPHY IN CHILDREN WITH UNILATERAL SEGMENTAL RENAL SCARS. H. Olbing on behalf of the International Reflux Study in Children.

Renal length, parenchymal projection area, and parenchymal thickness at the poles and the upper lateral segments have been measured (i.v. urogram) at entry, after 18 and 54 months in 402 european children with primary vesicoureteral reflux (VUR) grade III or IV. Hypertrophy was defined as > +2.0 SD (i. Claesson et al. 1978, 1980) of at least one parameter.

Among the 91 pts with unilateral scars (C.J. Hodson, S. Wilson, 1965) at entry, contralateral hypertrophy was demonstrable in 15 at entry and in 15. resp. 18 after 18 resp. 54 months. In patients with hypertrophy, the SD score correlated with the type (J. Smellie et al. 1975) of contralateral scarring and with age. Even from 14 patients with severe scarring (types C, D), 10 had no hypertrophy. Scarred kidneys as well as their unscarred twins maintained their SD score as long as no new scar developed.

The frequency of hypertrophy in the group with bilateral VUR was not smaller than in the group with unilateral VUR.

Our data suggest that kidneys without hypertrophy contralateral to renal scars cannot be considered as normal. We conclude, that they have been exposed to noxious conditious, for which the nature and the sensitive exposure period have to be identified.

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EFFECT OF AGE AT NEPHRECTOMY ON LONG-TERM CHANGES OF RENAL FUNCTION OF UNILATERALLY NEPHRECTOMIZED RATS.
P. Baudoin, A.P. Provoost, M.H. De Keijzer and E.D. Wolff.

We have reported that unilateral nephrectomy (uNx) in rats at the age of 6 weeks eventually results in renal failure. The period of stable GFR and the rate of fall of GFR were affected by dietary protein intake. Proteinuria preceded the decline of GFR. Young and adult rats respond differently to uNx. This may affect the long-term outcome.
We have compared long-term effects of uNx at the age of 3 (uNx3) with 15 weeks (uNx15) in rats fed 12% (LP), 24% (NP), or 36% (HP) protein diets. Groups initially consisted of 15 rats. Every 12 weeks, the GFR (plasma clearance of ^{51}Cr-EDTA) and urinary protein excretion (Coomassie blue) were assessed.
The GFR of rats on different dietary protein intake and the same age at time of uNx were significantly different. No differences between GFR in uNx3 vs uNx15 were found. However, uNx3 rats on an HP diet initially had significantly higher proteinuria than uNx15 rats. The uNx3 rats on an LP or NP diet had significantly higher proteinuria at 24 and 36 weeks post-uNx. Comparing the period of stable GFR of uNx3 and uNx15 rats, indicated that the lengths of these periods were significantly shorter in uNx3 rats (63 ± 18 vs 77 ± 20(wks) on LP, 33 ± 12 vs 45 ± 22(wks) on HP, 24 ± 14 vs 39 ± 12(wks) on HP). Significant effects of protein intake on the length of stable periods were present. No significant differences in the rate of fall of GFR between uNx3 and uNx15 rats were present (-0.17 ± 0.08 n=10 vs -0.19 ± 0.08 n=5 (ml/min*12 wks) on NP, -0.35 ± 0.15 n=13 vs -0.37 ± 0.08 n=5 (ml/min*12 wks) on HP; uNx3 vs uNx15). On LP diet not enough rats with a fall of GFR were available to determine the rate of fall. The rate of fall of GFR on HP diet was significantly higher than on NP diet.
We conclude that uNx3 and a high protein intake negatively affects the length of the period of stable GFR post-uNx. A high protein intake, but not the age at uNx, negatively affects the rate of fall of GFR.

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SINGLE KIDNEY IN CHILDREN: ITS FATE FOLLOW-UP
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We present the results of 53 children, followed-up after unilateral nephrectomia in the close (2-4 weeks) and after the prolonged time period(1-25 years). The prognosis in children with single kidney depends on the cause for ablation of controlateral one.After nephrectomia, performed because of trauma or tumour presence or renal agenesis,the remaining kidney usually stays intact. After nephrectomia in cases of pyelonephritis the mentioned maladie is known to progress further on. Such indices as glomerular filtration rate, osmotic concentration and ability to compensate for metabolic acidosis, are known to reach the levels in the only remaining kidney,observed routinely in both intact kidneys, as seen in the close post-operational period (7-14 days).After prolonged period (1-25 years) the functions of the single intact kidney were not found to differ from those in 2 intact ones.We have found the glomerular filtration rate and ability to compensate for metabolic acidosis in patients with a single-kidney-pyelonephritis to be restored after the same time period,as observed in children with single intact kidney,but the indices of osmotic concentration were markedly lower,than in the latter. Independently from the condition of remaining kidney character of renal hypertrophy was irregular.Renal volume increase was most intensive during first 3-6 months after the performed nephrectomia and seemed to occur mainly in lateral and inferior kidney segments.

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RENAL FUNCTION IN SICK PRETERM INFANTS: INFLUENCE OF GESTATIONAL AGE AND COLLOIDS

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In preterm infants hemodynamics and water balance are unstable and disturbances in renal perfusion are common. Fresh frozen plasma (FFP) has been used to stabilize blood pressure (BP), which might also have a positive effect on renal function. We studied the influence of FFP on renal function in two groups of preterm infants in intensive care: group I = G28 (GA <30 wk) and group II = G32 (GA 30-34 wk). The infants were randomly assigned to one of two treatment groups, one receiving FFP, the other not: G28-0 (n=9, 27.8 wk, 1128 g), G28-FFP (n=11, 27.8 wk, 1007 g), G32-0 (n=10, 31.9 wk, 1752 g) and G32-FFP (n=10, 31.8 wk, 1780 g). Infants in the FFP groups received FFP 10 ml/kg daily on days 1 to 3 during a two-hour period. Renal function was measured on days 2 and 5 and BP daily.

FFP did not influence renal function or BP either in G28 or G32. GFR (creatinine clearance) in G28 was lower than in G32 on days 2 and 5 (G28: 6.1±3.0 and 7.0±3.7; G32 10.0±4.3 and 13.6±4.4 ml/min/1.73m^2, $p<0.001$). FE-Na (%) was highly variable in G28 on day 2 (1.4-17.1%) and higher than in G32 (6.9±4.7 vs 2.4±1.7%, $p<0.01$). By day 5 FE-Na in G28 decreased to the same range as in G32 (4.1±1.4 vs 2.5±1.2%). P-Na (days 1 to 5) was equal in all groups with only a few hypo- and hypernatremic values. Hyponatremia was not related to high FE-Na. Hypernatremia was related to excessive weight loss. FE-K (days 2 and 5) was higher in G28 than in G32 ($p<0.01$). P-K (days 1 to 5) was higher in G28 than in G32 ($p<0.01$). Thus preterm infants with a GA <30 wk have a very immature and variable renal function during the first few days of life. Colloids do not improve renal function in preterm infants in intensive care.

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RENAL HANDLING OF SODIUM, WATER, PHOSPHATE AND IONISED CALCIUM IN PRETERM INFANTS

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In forty immature and mature newborns with conceptional ages ranging from 29 to 40 weeks 10-14 days after birth the glomerular filtration rate expressed by the renal clearance of inulin, the tubular reabsorption of sodium (T_{Na}/C_{In}), phosphate (T_P/C_{In}) and ionised calcium (T_{Ca}/C_{In}) have been measured. Osmolar and free water clearances (C_{osm} and C_{H_2O}) have also been calculated determing overall renal fluid handling at different stages of maturation.

At the end of second week of life infants of all ages showed a well established glomerulotubular feedback for renal handling of sodium, calcium and phosphate. Renal losses for sodium were calculated at 2,4 mmol/kg BW x d, so that no additional supplementation to original preterm formula turned out to be necessary. Renal losses of phosphate and calcium were low (1,97 and 1,12 mmol/d x 1,73 m^2). In parallel to increasing GFR with maturation (C_{In} from 23,5 to 34,2 ml/min x 1,73 m^2) total fluid handling improved with relative increase of C_{H_2O}. For two weeks old infants of 30-32 weeks conceptional ages the sum of C_{osm} and C_{H_2O} amounts to 131 ml/kg x d. The calculated renal fluid turnover rate increased to 200 ml/kg x d in mature infants. At the age of two weeks infants of more than 30 weeks conceptional age maintain a glomerulotubular balance despite glomerular insufficiancy.

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RELATIONSHIP OF URINARY ALBUMIN TO GLYCOSAMINOGLYCAN (GAG) EXCRETION IN INFANTS DURING THE FIRST YEAR OF LIFE

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The present study was undertaken to investigate the age-related changes in urinary albumin and GAG excretion in 32 healthy infants during the first year of life. To identify individual GAG components purified GAGs were digested with specific lyases followed by HPLC separation and quantitation. Urinary albumin excretion was determined by using RIA method.

Urinary albumin excretion expressed in term of body surface area declined steadily with advancing age, while there were no apparent alterations in the excretion of total and individual GAGs. Urinary albumin excretion correlated positiely with the excretion of total GAG ($r=0.61$, $p<0.001$, hyaluronic acid ($r=0.59$, $p<0.001$) and chondroitin ($r=0.64$, $p<0.001$), whereas no significant relationship of albumin excretion to chondroitin-4-sulfate, chondroitin-6-sulfate, heparan sulfate and dermatan sulfate excretion could be detected.

It can be concluded that physiological microalbuminuria of infancy is causally related to the high rate of GAG, in particular the non-sulfated GAG excretion. Since induvidual GAG compounds of glomerular basement membrane (GBM) in newborn and adult rats were found to correlate positively with the respective GAG species in the urine, the albuminuria-related changes in urinary GAGs can be assumed to reflect alterations in GAG composition of GBM that occur in infants with albuminuria.

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ACUTE RENAL FAILURE IN A NEONATAL INTENSIVE CARE UNIT

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Acute renal failure (ARF) in neonates admitted to an I.C.U. represents a major problem.Important questions are still partly solved: 1.What is its real incidence?,2.What are the most prevalent pathogenesis ?,3.What are the main applicable diagnostic criteria?, 4.What is the best care to prevent water and electrolytes imbalances in these very severe ill newborns?In order to answer to these questions we are currently conducting a propsective study in our ICU and we present here the results referring to one year (89).

I. 30/193 neonates (15.5%) presented with ARF.In 15/30 , ARF was oliguric. 11/30 were term babies.

II.We identified the following main causes for ARF : 1. Hypotension (12). 2.Asphyxia (9),3.Hypoxaemia (3), 4.Sepsis (3), 5.Miscellaneous (3).Hypotension and/or asphyxia were often associated with hipoxaemia.

III. 46.7% of all neonates with ARF presented with Na_s less than 130 mmol/l and 53.3 % with K_s above 6.0 mmol/l.

IV.11/30 newborns with ARF (36.6.%) died. 7 out of these 11 babies presented with hypotension associated to severe respiratory disease. The overall mortality of the ICU in the same year was 14.0 %.

An early and careful diagnosis of ARF and a precise water and electrolytes management is mandatory.

Actually,we consider this management the most difficult problem to deal with in newborns admitted to an ICU .

More clinical research is needed in this area.

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RENAL FUNCTIONAL RESERVE(RFR) IN CHILDREN WITH REFLUX NE - PHROPATHY(RN) AND IN CHILDREN WITH TYPE I DIABETES(IDDM).

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We have studied RFR in 7 children with RN(mean age 8.8y., all females)(Group I) and in 8 children with IDDM(mean age 11.7y.,3M-5F,mean duration of disease 6y.)(Group II):7 were well controlled except a 13y. and 8mo. old girl(A.R.) with diabetes lasting from 4y. She was the only patient with microalbuminuria. In all groups creatinine clearance was normal. Controls were 9 healthy children. RFR has been valuated by measuring the modifications of the creatinine clearance(dClcr) and of the creatinine excretion rate(dCER) after a protein meal. Results are expressed as % of the baseline values. The amount of protein-bolus,given as baked chicken,was equivalent to the 10% of the daily caloric requirement. The T-Student's test was used for statistical analysis. Results may be summarized as follows:

Control group: mean dCER was 71.43±19.39(range 45.05-103.4) mean dClcr:39.73±29.05(range 4.87-83.04).

Group I (RN): mean dCER was significantly lower than in controls (28.7±14.07,range 12.5-51.9,p<0.0001). Mean dClcr was 24.92±20.13,range from -1.98 to 55.98(p<0.09).

Group II (IDDM): in 4 patients dCER was above 45% (108;70.8 83.3;45.2 respectively) which is the lowest value observed in our controls. This value is similar to the one obtained by Hellerstein et al.(48.2%). In the other four patients dCER ranged from -3.6 to 21 and dClcr from -10.7 to 21.6. The lowest values in this soubgroup were observed in A.R. Mean dCER was 43.73±39.86,range from -3.6 to 108;mean dClcr was 27.72±23.22,range 10.71-67.56.

RFR may be useful to detect early kidney disfunction.

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RENAL EXCRETION OF CITRATE DURING CHRONIC METABOLIC ALKALOSIS IN INFANTS

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The increase in renal excretion of citrate (Ci) in alkalosis has been suggested as a marker of intracellular decrease of Ci oxidation. The present study was performed to assess the role of changes in the renal excretion of Ci a metabolic precursor of bicarbonate, in modulating the acid-base balance in chronic alkali loading in infants.

Normal infants (14) aged 3-12 months were studied before and during 5 days of oral $NaHCO_3$ administration, 157,0 mM/1,73 m^2/day. During alkali loading period the blood acid-base parameters showed the mild compensated metabolic alkalosis. Alkalinization resulted in a significant hypercitratúria (FECi 41,0 + 5,4 vs. 16,4 + 2,6 % in control period) that was in the positive relation to marked increase in $FEHCO_3^-$, FENa and urinary pH values. The renal excretion of Ci (UCiV) varied inversely with the renal excretion of H^+ ($p< 0,001$). The index of UCiV/UH+V rosed from 1,1 % in control period to 7,7 % in the 5 day of alkali administration.

It is concluded that hypercitratúria in chronic metabolic alkalosis is one of the several mechanism whereby an increased base load is dissipated. The determination of urinary Ci versus urinary H^+ may serve as an additional index in the renal acid-base contribution during chronic metabolic alkalosis in infants.

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MICROALBUMINURIA IN INSULIN-DEPENDENT DIABETIC CHILDREN: MEASUREMENTS BY RIA AND ELISA DURING METHABOLIC DECOMPENSATION AND AFTER CONTROL OF HYPERGLYCAEMIA

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The detection of microalbuminuria (MIA), i.e. increased urinary albumin excretion above the normal range but still undetectable by routinary assays, it thought to reflect an incipient stage of nephropathy that precede the development of overt proteinuria and progression to renal failure. Sporadic observations suggest that in adult diabetics rigorous control of hyperglycemia can reduce urinary albumin excretion (UAE) during the incipient stage of diabetic nephropathy. Several methods have been proposed to detect MIA. Radioimmuneassays (RIA) and enzyme linked immuno sorbent assays (ELISA) seem the most reliable tecniques.

Aim of this study was to evaluate 9 children (5 males, 6.10-13.15 years-old) affected by type I diabetes, admitted to our hospital because of the first discovery of diabetic metabolic decompensation. After 2 months of control of hyperglycemia, the children were studied again.

UAE was measured in overnight urine collection on three consecutive nights by two different test, a commercially available RIA (Pharmacia) and an ELISA previously published by our group (Journ Diab Complic 1: 58, 1987). A mean of the three measurement was considered the UAE excretion.

In phase of metabolic decompensation UAE values were 1.66 ± 1.01 µg/min by RIA and 1.52 ± 2.16 µg/min by ELISA non significantly different from controls and from data obtained after glycemic control.

However, in a subgroup of 5 children UAE significantly decreased after insulin control of hyperglicemia from 1.90 ± 1.1 µg/min to 1.07 ± 0.60 ($p<0.02$) by RIA and from 1.68 ± 2.33µg/min to 0.49 ± 1.07 µg/min ($p<0.05$) by ELISA.

RIA and ELISA individual values of UAE were highly significantly correlated ($r=0.59$, $p<0.0001$).

In conclusion our data indicate that both RIA and ELISA tests provide valuable data for measuring UAE in diabetic children and the results given by these methods are significantly correlated. During acute methabolic decompensation at the first discovery of diabetes we id not detect overt microalbuminuria. However, the finding of decrease in UAE after control of hyperglicemia suggests that UAE values at the beginning of the clinical hystory can reflect glomerular hemodynamic alterations leading to glomerular hyperfiltration

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BIOCHEMICAL EVALUATION OF SECONDARY HYPERPARATHYROIDISM IN CHILDREN WITH CHRONIC RENAL FAILURE

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Secondary hyperparathyroidism is an inevitable consequence of untreated chronic renal failure (CRF) in childhood. Assessment by measurement of plasma total calcium (tCa), phosphate (P), C-terminal parathormone (C-PTH), alkaline phosphatase (ALP), %tubular reabsorption of phosphate (%TRP) and bone radiographs can be difficult to interpret. We have evaluated the relationship of these parameters with ionised calcium (Ca^{2+}) and intact PTH (i-PTH) in 98 children with CRF (plasma creatinine (PCr) 333±167 (SD) µmol/l). There was a positive correlation ($r=0.60$, $p<0.05$) between PCr and C-PTH but none with i-PTH. There was a correlation between Ca^{2+} and tCa ($r=0.60$, $p<0.05$) with Ca^{2+} being 49.2±4.0 (SD) % of tCa. There was no correlation between C-PTH and tCa but there was suppression of i-PTH secretion with tCa of >2.2 mmol/l ($p<0.001$). With tCa of >2.6 mmol/l and a raised i-PTH (>80ng/l), Ca^{2+} was normal in 66% of samples. There was no correlation between i-PTH and ALP or %TRP. Renal osteodystrophy score correlated with ALP and i-PTH ($p<0.05$). These results suggest that the C-PTH assay mainly reflects renal function and should be replaced by that for i-PTH which demonstrates a response to hypocalcaemia independent of renal function. They also point to a role for Ca^{2+} determinations in evaluating states in which tCa and i-PTH are both raised.

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PHOSPHATE DIALYSIS REMOVAL (PDR) : ENHANCEMENT OF PHOSPHATE CELLULAR CLEARANCE BY BIOFILTRATION (FREE BUFFER DIALYSATE)

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PDR depends in part on the type (acetate or bicarbonate) and the concentration of the dialysate buffer. Biofiltration (BF) with free buffer dialysate and molar bicarbonate infusion allows bicarbonate modelling. Plasma phosphate (P) reduction during a dialysis treatment is the algebrical result from PDR, from phosphate cellular flux (captation or excretion) and from phosphate tissular precipitation. High bicarbonate plasma levels induces intracellular shift of phosphate, thus no available for dialytic removal. Acidosis on the contrary prevents P shifting into the intracellular space, thus more P is available for dialytic removal. We evaluate PDR (three and half hour session) in three children, mean weight 27kg (22-33kg) treated successively (n=6) with either constant infusion rate of bicarbonate infusion (BF) or initial (first half hour session) low steep of bicarbonate infusion rate (sequential BF : SBF). PDR is significantly higher in SBF (32 ± 4mmol per session, n=18) as in BF (24 ± 6mmol per session, n=18). During the first half hour session PDR is also significantly higher in SBF (8 ± 2.6mmol, n=18) as in BF (5 ± 2.4mmol, n=18). These results can be directly correlated with P cellular flux, specially during the first half hour session. In SBF, PDR is secondary to extracellular removal (ECR : +6 ± 2mmol) and intracellular removal (ICR : +2 ± 1.4mmol). On the contrary in BF, PDR is lowered by intracellular phosphate shift (-4 ± 1.8mmol).
BF allows bicarbonate modelling during dialysis treatment. SBF prevents P shifting into the intracellular space, this enhances PDR. The practical application for SBF are under further investigations.

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BIOELECTRICAL IMPEDANCE ANALYSIS (BIA) IN THE ASSESSMENT OF BODY WATER AND BODY COMPOSITION IN CHILDREN WITH RENAL DISEASE.

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Tetrapolar BIA has been introduced as a new non-invasive method to assess total body water (TBW) and body composition (lean body mass, LBM). In order to validate this technique in renal disease, we measured bioelectrical impedance in children on hemodialysis (HD), on continuous ambulatory peritoneal dialysis (CAPD), and with nephrotic syndrome (NS) in the edematous state and after remission. In 10 children on HD, repeated measurements were performed in 30 min intervals during 17 4-hour HD sessions. A very high correlation between ultrafiltration rate and BIA was observed ($r=0.93$, $p<0.0001$). In contrast, studies in 6 patients on CAPD during 9 dialysate exchanges revealed no significant change of TBW as estimated by BIA by instillation removal of dialysate fluid. In 21 patients with acute NS the effect of forced diuresis by albumin and furosemide infusion on TBW was evaluated by BIA in 10 min intervals. We found a tight linear relationship between diuresis and shrinkage of BIA-derived TBW. BIA changed significantly well before and some time after the appearence of edema. In patients followed over extended periods of time (1 month-1 year) the correlation between TBW and weight changes ($r=0.71$, $p<0.001$) was not as close as in acute HD or in edema, probably because BIA was additionally influenced by growth-related changes of LBM.
In summary, BIA is a sensitive technique to evaluate acute changes of body water content. As it does not differentiate between interstitial fluid and changes of LBM, it is of limited usefulness in the long-term monitoring of edema in growing children. When LBM is to be determined by BIA in patients with renal disease, no acute edema should be absent.

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CARDIORESPIRATORY AND METABOLIC RESPONSE TO EXERCISE IN DIALYSED CHILDREN TREATED BY rh-ERYTHROPOIETIN (EPO)

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Maximal working capacity (Wmax) and maximal oxygen uptake ($\dot{V}O_2max$) are severely reduced in dialysed children compared to healthy controls (C). Despite its benefits it is questionable if EPO is able to completely restore normal aerobic and anaerobic capacities. We applied bicycle spiroergometry in 5 children aged 9 - 16 yrs on regular dialysis. The workload was increased stepwise by 0.5 W/3min up to exhaustion. Various cardiorespiratory parameters and blood lactate (L) were measured continuously. In addition some plasma hormones were determined at rest and at Wmax. The table presents the relevant changes observed before (B) and after (A) administration of EPO (Cilag, 75 - 300 u/kg/week) for 6 - 10 weeks, when the target level was reached (median values)

	Hb g/dl	Serum K at Wmax mmol/l	Wmax W/kg	$\dot{V}O_2max$ ml/min/kg	Total Work KJ/kg	VAT[1] %	Qmax[2] l/min/kg
B	7.2	5.0	1.90	2.59	0.99	83.5	0.39
A	10.3	5.7	2.88	3.48	1.56	86.5	0.21
p =	0.01		0.01	0.03	0.07		0.03

1 Ventilatory anaerobic threshold (VE/VO2) in % of VO2max (norm=83)
2 Cardiac output at Wmax

Wmax and $\dot{V}O_2max$ reached only 83 % and 79 % of values in C, respectively. During increasing workload heart rate and blood pressure were slightly lower in A vs. B, whilst $\dot{V}O_2$ was similar. L production in A initially lagged behind that in B, and at Wmax the lactate threshold of 4 mmol/l was reached only in 2 cases. Plasma noradrenalin levels were decreased before and after exercise in B and were even lower in A. These findings suggest that by EPO therapy both aerobic and anaerobic working capacities are improved but not normalized. Persistently reduced adrenergic activation of glycolysis in muscle associated with blunted L production might explain why respiratory functions are not normalized after EPO.

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RECOVERY OF LEFT VENTRICULAR FUNCTION AFTER RENAL TRANSPLANTATION IN CHILDHOOD

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The heart disease induced by chronic renal failure (CRF) and by long-term dialysis (D) was reported to be irreversible in adult patients. Little information is available concerning the prognosis of cardiac function in pediatric patients with CRF after successful transplantaion (TP). Mechanocardiography, by measuring systolic time intervals, has proved to be a valuable tool for evaluating left ventricular function (LVF) : an increased ratio of the pre-ejection period (PEP) to the left ventricular ejection time (LVET) indicates left ventricular impairment. We analysed the mechanocardiographic findings in 26 pediatric patients repeatedly 1 - 7 (mean 3.5) years before and 4 - 13 (mean 6) years after TP. Mean duration of dialysis was 2 (0.5 - 5) years. Serum creatinine levels ranged from 0.9 to 4.5 (mean 1.8) mg/dl at the latest observation. PEP/LVET was increased in 24% of patients with preterminal CRF (n = 21), and in 33% during dialysis (n = 24). At 5 - 20 (mean 12) months after TP (n = 23), 17 % presented impaired LVF , and at 2.5 - 6.5 (mean 4.5) years after TP (n = 25), only one patient (4%). We conclude that in pediatric patients uremic heart disease usually resolves after successful TP, although the time for recovery often requires many years.

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EXERCISE TOLERANCE IN CHILDREN WITH CHRONIC RENAL FAILURE.

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Aim of the study: evaluate the response to a maximal stress test in patients (P) in chronic renal failure (CRF), in hemodyalisis (HD), and after renal transplant (Tx).

Material and methods: P examined: 6 in CRF (3 M, 3 F), mean age 10,9 years (range 6,5-17 y; range GFR 8,3-42,1 ml/min/1,73 sqm), 8 in HD (5 M, 3 F), mean age 14,3 y. (range 9-18), and 10 after Tx (7 M, 3 F), mean age 16,2 y. (range 6-22). All P underwent: clinical evaluation, blood pressure (BP) and ECG. at rest, maximal exercise testing on treadmill (modified Bruce protocol).

Parameters examined during the test: duration (min.), maximal blood pressure (BP max) and heart rate (HR max). The results of exercise testing were compared separately, and in each class of P, with those obtained from a group of healthy children of same chronologic age (CA) and with an other with same body surface area (BSA). The majority of P presented a reduction of body size.

Results: are summarised on the table:

EXERCISE TESTING

	CRF	CA BSA	HD	CA BSA	Tx	CA BSA
DURATION (min)	12.3±3.7	12.6±1.1 12.4±2.9	8.6±1.9	14.3±1.5 13.4±2.5	10.6±2.6	13.5±1.6 12.7±1.7
HR Max	190.8±10.2	202.3±8.5 192.6±8.9	178.5±18.1	198.6±10.6 194.6±8.5	188±9	195±7 193±12
BP Max	147±25	133.5±13.6 126.8±8.7	140.2±18.3	145.7±17.6 134.7±9.9	175±25	157±26 136.5±15.2

Significant reduction of exercise tolerance in P in HD in comparison to CA and BSA and in P after Tx in comparison to CA. In this group BP max significantly higher in comparison to CA and BSA.

Conclusions: P with CRF present ergometric patterns similar to healthy children; P in HD a reduction of exercise tolerance; P in Tx a reduction of exercise tolerance only with respect to peers, but a costant hypertensive response which has to be considered carefully for the partecipation to a strenuous physical activity.

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THE EFFECT OF CYCLOSPORINE A (CSA) ON ARACHIDONIC ACID AND PROSTAGLANDIN BIOSYNTHESIS IN CULTURED HUMAN SKIN FIBROBLASTS.

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The administration of CSA to patients may induce renal nephrotoxicity. Renal vasoconstriction, vascular and cell damage has been implicated in this process. The purpose of the study was to estimate the influence of CSA on the production of arachidonic acid (AA) and prostaglandins (PG) in cultured human skin fibroblasts (HSF) model. Basal eicosanoid biosynthesis was determined in Hank's solution containing various concentrations of CSA (250, 769, 1667, $5 \cdot 10^3$, 10^4 ng/ml) after preexposure of the cells for 30 min. Bradykinin (BK) effect on PG and AA release was examined by following 5 min BK stimulation in the presence of CSA. CSA dose dependently inhibited basal 6-oxoPGF1a, PGE2 and TxB2 release after 30 min preexposure time, as compared to respective controls. 6-oxo PGF1a and TxB2 release was not significantly suppressed at the lowest chosen CSA concentration. Basal AA production was not effected at the concentration of 250-1667 ng/ml CSA. However, at the concentration of 5000-10000 ng/ml CSA, AA release was singnificantly increased and morphologically damaged cells were observed. BK stimulated PG and AA synthesis was inhibited by CSA dose dependently.

The results indicate that CSA inhibits both basal and bradykinin evoked PG and AA release from HSF by impairing the availability of free arachidonic acid rather than by inhibiting the convertion of AA into prostaglandins.

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URINARY EXCRETION OF C3 DECAY PRODUCTS AND MEMBRANE ATTACK COMPLEX (MAC) IN CHILDREN WITH KIDNEY TRANSPLANTS (Tx)

A.-M.Wingen, C.K.Keller, R.Deppisch, K.Schärer

In most biopsies of patients with Tx rejection we observed co-localized deposits of C3d and MAC along glomerular and tubular basement membranes. Urinary excretion (Uex) of C3d and MAC without concurrent systemic complement activation may reflect local complement activation in the kidney. Therefore, we developped three highly sensitive double sandwich ELISA systems able to measure C3, C3d and C5b-9 complexes (MAC) in unconcentrated urines. We screened 150 24h-urines and plasma samples taken in parallel of 48 children with Tx. No correlation was found between plasma concentrations (U/ml) and Uex (U/1.73m2/day) of C3d and MAC. This may indicate local complement activation in the renal tissue. C3d and MAC concentrations were not correlated to tubular and glomerular proteinuria, respectively. Initially after Tx C3d Uex was high, normalized with improving renal function and again rose to high values in case of rejection. Similarly, in children 1 - 8 years after Tx the C3d Uex was inversely correlated to graft function. A high Uex of MAC was exclusively found during rejection episodes and in one patient with de novo epimembranous glomerulonephritis in the graft. But, though MAC Uex was significantly correlated to C3d Uex we could not find any significant correlation between MAC Uex and graft function for the cumulated data of all patients. Our results suggest a local C3 activation in acute and chronic deterioration of graft function which does not necessarily lead to the formation of MAC. The mechanisms of complement activation and their influence on graft function are unknown.

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INCREASED BIOSYNTHESIS OF VASOACTIVE PROSTANOIDS IN ACUTE RENAL ALLOGRAFT REJECTION

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Acute renal allograft rejection has been associated with altered biosynthesis of vasoactive prostanoids. Thromboxane (Tx) A_2 is a potent platelet agonist and vasoconstrictor, which may contribute to the decline in renal blood flow (RBF) and GFR during rejection, whereas prostaglandin (PG) E_2 and prostacyclin (PGI_2) may counteract by their vasodilative properties. To address this hypothesis, 10 children (aged 3-19 years) were studied prospectively in the first six weeks after renal transplantation. Prostanoid biosynthesis was quantified by measuring urinary excretion rates of stable index metabolites using gas chromatography/mass spectrometry.

In 13 rejection crises TxB_2 excretion increased from basal median 9.1 (range 0.5-18.6) ng/h/1.73 m^2 significantly ($P<0.005$) to 19.7 (range 1.6-133) ng/h/1.73 m^2 one to two days prior to clinically apparent acute rejection. Urinary TxB_2 was reduced but not normalized by steroid pulse therapy. A similar pattern was obtained for urinary 2,3-dinor-TxB_2 excretion. Urinary PGE_2 increased from basal 14.2 (range 2.5-43.3) ng/h/1.73 m^2 to 22.5 (range 4-55.3) during rejection. In contrast, urinary PGI_2 metabolite excretion was not elevated. Renal TxA_2 formation was not altered in histologically proven chronic rejection and by cyclosporine A when compared to an azathioprine treated group. Our data demonstrate increased renal TxA_2 biosynthesis prior and during acute renal allograft rejection, which is likely to potentiate the loss of RBF and GFR. In contrast, increased renal PGE_2 formation appeares to be renoprotective by mediating vasodilation and stimulating salt and water excretion.

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INCREASED URINE HEPARAN TO CHONDROITIN SULPHATE RATIO IN CHILDREN WITH CONGENITAL NEPHROTIC SYNDROME (CNS)

L Jadresic, G Filler, T M Barratt

Vernier et al observed a reduction in the number of anionic sites in the glomerular basement membrane (GBM) of children with CNS, and Vermylen et al reported decreased heparan sulphate (HS) in the GBM of a child with CNS associated with diffuse mesangial sclerosis (DMS), though in this and 3 other children with CNS (DMS 1, Finnish-type CNS (FCNS) 2) urinary excretion of HS was raised in relation to chondroitin sulphate (CS): they postulated a defect in the assembly of HS into the GBM in CNS. We investigated the specificity of the urinary HS/CS ratio in 21 childen with CNS: FCNS (7), DMS (6), and focal segmental glomerulosclerosis (FSGS) (8), together with 17 controls and 16 older children with minimal-change nephrotic syndrome (MCNS). We measured urinary total glycosaminoglycans (GAG) by Alcian Blue precipitation and separated HS and CS by cellulose acetate electrophoresis. Urinary GAGs and albumin (UA) were related to creatinine (UC) (mg/mmol):

±SD	Normal	FCNS	DMS	FSGS	MCNS
Age	3.1±2.9	0.8±0.6	1.6±1.9	3.5±2.9	9.6±4.7
UA/UC	0.05±0.05	56±65	41±50	20±13	5.2±5.3
GAG/UC	1.3±0.4	9.1±16.8	2.6±1.5	1.6±1.5	0.8±0.9
HS/CS%	38±13	82±30	71±21	81±38	44±12

The urinary HS/CS ratio was independent of age. Mean urinary HS/CS was significantly greater in FCNS, DMS and FSGS than in controls or older children with MCNS ($p<0.001$). 5/7 FCNS, 3/6 DMS and 3/8 FSGS but only 1/16 MCNS children had values for urinary HS/CS 2SD above the mean of the normals. The data confirm the raised HS/CS in CNS, but show it not to be specific for a particular histological subgroup.

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MOLECULAR ANALYSIS OF CHROMOSOME REGION 11p13 IN PATIENTS WITH DRASH SYNDROME

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The association of nephropathy, Wilms' tumour and genital abnormalities is known as Drash syndrome. Two of these features are also seen in children with aniridia, genitourinary abnormalities, mental retardation associated Wilms' tumour (WAGR complex), known to be associated with deletions of chromosome region 11p13.

We have carried out karyotypic and molecular studies in 11 Drash patients, 5 males and 6 females. All males had a 46XY karyotype as did 4/6 phenotypic females, the other two childen having a 46XX karyotype. One of the 46XX females also had a deletion of region 11p13-p12, the only detectable autosomal chromosome abnormality in any of the patients studied. Lymphoblastoid cell lines were prepared from six of the Drash patients and were used in dosage studies using a variety of DNA probes from the 11p13 region. There was no evidence in any patient with a normal karyotype of microdeletions. Because of the 46XY karyotype prevalence in this disorder several X chromosome loci were analysed and all found to be normal.

Although Drash syndrome is likely to genetic in origin there are no readily detected deletions within the 11p13 region.

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ULTRASOUND CHARACTERISTICS OF CONGENITAL NEPHROSIS OF THE FINNISH TYPE

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Ultrasonographic follow up study was performed on 9 cases of congenital nephrotic syndrome of the Finnish type (CNF) in order to characterize typical US- features of the affected kidneys. The following characteristics of the nephrotic kidneys were documented: a) kidney's size and outlines, b) echogenicity of kidney parenchyme: cortex and medulla, c) corticomedullary differentiation, d) central echo, e) pyelocaliceal system. The ultresonographic features of kidneys in patients with CNF typically changed within the first year of life:

1/ Early stages of the disease (first month of life): Kidney's size and outlines are unchanged. Hyperechogenicity of kidney's cortex with marked corticomedullary differentiation and suppression of medullae are present. Central echo is not clearly defined, because it merges with hyperechogenic cortex. Kidney's cavities seem to be normal.

2/ Later stage of the disease (after the first month of life): Kidneys are mostly enlarged, but with regular outlines. In the second half of the first year of life gradual enlargement of the renal cortex is present causing the suppression of the medullar structures. Corticomedullary differentiation progressivelly disappears, causing the hyperechogenic impression of the whole kidney parenchyme. Central echo can not be defined. Kidney's cavities seem to be normal. These ultrasonographic features and their changes within the first year of life have proved to be of great help in reaching the diagnosis.

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COMPARISON OF HLA-DRß TYPING BETWEEN FRENCH AND GERMAN PATIENTS WITH IDIOPATHIC NEPHROTIC SYNDROME (NS)

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The occasional familial occurrence of NS points to a genetic predisposition. Differences in the frequencies of certain HLA-antigens between NS pts and healthy controls(C) support this hypothesis. Previously we found an increased frequency of HLA-DR3 and HLA-DR7 in NS. As conventional serological HLA-DR typing is not able to detect the full range of DR-polymorphism we applied the Restriction Fragment Length Polymorphism (RFLP)-method. We compared the DRß allele frequencies of pediatric NS pts from Heidelberg (HD,n=57) and Toulouse (T,n=61). We found increased frequencies of DRß7.1 in all steroid sensitive (SS) pts (HD:28% vs 4% in C, T:50% vs 10%). DRß6 and DRß15 were decreased in both SS-NS populations. DR1/Br (36% vs 17%) and DR17.1 (36% vs 17%) were increased only in SS pts from HD. In contrast steroid resistant (SR) pts showed an increase of DRß17.2 (HD: 13% vs 3%). All these differences were significant. The data support the hypothesis that SS and SR pts with NS have not the same immunogenetic background. The pattern of HLA-DRß Typing is similar in the two populations studied only for the SS group. Supported by DAAD.

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ADRIAMYCIN IS CYTOTOXIC ON GLOMERULAR EPITHELIAL CELLS WITHOUT ENTERING THE CELL. A NEW MODEL OF NEPHROTOXICITY MEDIATED BY DRUG CELL SURFACE INTERACTION. Ghiggeri G.M., Bertelli R., Ginevri F., Gusmano R.

Adriamycin (ADR) nephrosis is universally considered the animal model of human minimal change nephropathy and the comprehension of the mechanism of ADR nephrotoxicity is central to the understanding of the human disease.
We have investigated the site of ADR interaction with glomerular epithelial cells (GEC) "in culture" by developing a model of ADR-cell interaction without internalization of the drug. ADR was chemically linked to an agarose macroporous bed (40-210 µm in diameter) which prevented the cellular uptake of the drug and its cytotoxicity on GEC was evaluated by 1) morphology, 2) incorporation into DNA of 3H-thymidine, 3) trypan blue dye exclusion.
Equimolar amounts (7.5 µg/ml) of free and agarose bound ADR induced the same morphological alterations of GEC characterized by loss of their typical polyedric, cobblestone appearance and also induced a marked inhibition of 3H-thymidine incorporation (-40% and -42% respectively). Cell viability as determined by trypan blue exclusion was also similar in both models.
These results indicate that ADR exerts ith cytotoxic effect on GEC by interaction at the cell surface while the intracellular compartment, principally DNA, is not the target of the drug.
This evidence provides a new interpretative model for the mechanism of nephrotoxicity "in vitro" which can be concerned in the "in vivo" models of experimental nephrosis.

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CYCLOSPORIN A IN MCNS: CsA STUDY II OF THE ARBEITSGEMEINSCHAFT FÜR PÄDIATRISCHE NEPHROLOGIE
P.F.Hoyer for the APN

The aim of the study was to assess the efficacy, safety and tolerability of a 26 weeks course of treatment with cyclosporin A (CsA) in patients with MCNS who are steroid responsive and in whom frequent relapses with signs of steroid toxicity are still present despite a previous course with cytotoxic treatment. A 26 weeks course with CsA was compared with 26 weeks before and 26 weeks after CsA. Parameters of efficacy were the number of relapses and the cumulative dosis of prednison required for the treatment of relapses under 26 weeks of CsA treatment compared with 26 weeks before and after.
The CsA starting dosage was 150mg/m²/day, CsA 12h whole blood levels (monoclonal RIA) were adjusted to 80-160 ng/ml. Relapses were treated with prednison according to the standard relapse treatment protocol as defined by the APN.
Fourteen patients entered the study so far, 11 completed the study. The number of relapses per patients and 26 weeks was 4.2 before CsA treatment, 0.3 under CsA and 3.3 after CsA treatment.
The cumulative dosage of prednison decreased from 4030 mg/m² before CsA to 890 mg/m² under CsA, but was 4214 mg/m² after CsA.
The GFR under CsA remained stable, (C_{crea} before CsA = 101.6 ± 24 ml/min/1.73m², under CsA (in the 24th week) = 116.6 ± 33). No serious side effects were observed.
We conclude that CsA treatment is an effective alternative treatment for the severest form of steroid dependent MCNS.

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RENAL EFFECTS OF SYNTHETIC PAF-ACETHER INFUSION INTO THE RABBIT: A MORPHOLOGICAL STUDY.
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The platelet-activating factor(PAF,PAF-acether) exerts a wide spectrum of biological activity. Intrarenal infusion of this phospholipid have shown to induce the loss of glomerular polyanionic charges with proteinuria,whereas systemic administration of PAF in high doses leads to a schok-like events.
We studied the morphological changes in the kidney tissue after i.v. multiple injection of small and medium doses of PAF-acether into the rabbit. Five adult animals were taken in the experiment and four were controls.The solutions of PAF-acether injected into the rabbits ear vien 3 times daily during 4 days.The doses of PAF were: 1st day-50 ng/kg: 2d day-100 ng/kg: 3d day-250 ng/kg and 4th day- 500 ng/kg.The control rabbits received 0.9% NaCl only.
The severe injuries of renal tissue were found in PAF-treated animals compared with controls:
-blebs and retractions of vascular endothelium: vasospasm,perivascular interstitial oedema: the presence of intravascular platelet and neuthrophyl aggregates and thrombus
-hypercellularity both in glomeruli and interstitium represented mainly by infiltrating mononuclear cells
-fibrin deposition in interstitium and partly in mesangium.
Conclusion. The multiple injections of PAF-acether in small and medium doses induce the various morphological changes in the rabbit kidney. Many of them are similar to those in experimental and human nephropathy.

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MINIMAL CHANGE NEPHROTIC SYNDROME (MCNS): LONG PREDNISONE THERAPY VERSUS STANDARD PREDNISONE THERAPY.

Arbeitsgemeinschaft für Pädiatrische Nephrologie (APN)
presented by J.H.H. Ehrich

In a controlled cooperative multicenter study two regimens of steroid treatment for the initial attack of MCNS were compared. In the experimental group a long prednisone therapy (60 mg/m²/24h for 6 weeks and 40 mg/m²/48h for 6 weeks) was given and in the control group a standard prednisone therapy (60 mg/m²/24h for 4 weeks and 40 mg/m²/48h for 4 weeks). Seventy-two patients with a first attack of MCNS were studied for a mean period of 20 months. Patients were allocated at random to long (n=35) and to standard therapy (n=37). Mean total prednisone dose for the initial attack was 3360 mg/m² in the Long-Group and 2240 mg/m² in the Standard-Group. The cumulative rate of patients with sustained remissions after 18 months was significantly higher after the long course than after standard treatment (47% vs 21%, p (0.006) and frequent relapses occurred less frequently after long treatment. Acute side effects of steroid therapy were seen more often after long therapy, however, these were mild and reversible in almost all patients of both groups. It is concluded that the initial immunosuppression determines the length of benefit from corticosteroid therapy in MCNS and that a longer prednisone treatment extending the standard regimen is justified.

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INAPPROPRIATE HYPERTENSION ASSOCIATED WITH HYPOVOLAEMIA IN THE NEPHROTIC SYNDROME (NS)

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Hypertension in NS is thought often to indicate the presence of a more serious underlying lesion than that of minimal change nephropathy. This is not necessarily the case if seen in the acute situation of a nephrotic relapse.

We report on two patients in acute relapse who had hypertension. Both patients had steroid-sensitive NS and became acutely hypertensive during a relapse. Both were on prednisolone at full dosage. There were clinical signs of hypovolaemia. Systolic blood pressure (BP) prior to plasma administration was 150 mmHg in both cases. In the first patient, aged 5 years, there was a progressive fall in BP to normal over the next 12 hours, associated with a fall in haemoglobin from 17-14 g/dl. In the second patient, aged 10 years, BP became normal over a period of days, and more colloid was given. Haematocrit fell from 0.43 to 0.35. Serial plasma renin activities measured during these periods were progressively 1075,285,307,0 and 1403,855,570 ngAI/l/hr for each patient respectively (normal range 130-830).

We believe that the inappropriately high blood pressure associated with clinical signs of hypovolaemia seen in a nephrotic relapse may be at least partly due to over-secretion of renin in response to an inadequate circulatory volume, and that plasma expansion, rather than antihypertensives, should be the priority. Also, our data would indicate that in these circumstances the absence of hypotension does not imply the presence of an adequate circulatory volume.

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NUTRITION AND LIPID PROFILES IN INFANTS WITH CONGENITAL NEPHROTIC SYNDROME OF THE FINNISH TYPE (CNF).

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CNF is an autosomal recessively inherited disease which today can be treated with renal transplantation. However, prior to transplantation poor growth may be a problem and atherogenetic lipid changes may influence the long term prognosis. We have studied growth, protein and lipid metabolism in ten nephrotic CNF patients (mean age 0.6y, range 0.15 - 1.95y). A diet with 130 kcals/kg/d, protein 4g/kg/d orally and albumin 4g/kg/d i.v., 10-15 ml vegetable oils and 2 ml fish oil, thyroxin, D2-vitamin, Ca, Mg, trace elements and water soluble vitamins was instituted.

The dietary recommendations were successfully carried out. Serum albumin (mean 24 g/l, range 13-32), protein (mean 46 g/l, range 28-59) and prealbumin (mean 108 mg/l, range 58-157) concentrations were low but plasma amino acids normal. Growth was normal (between +2 and -2SD) for age in all children. Apoproteins AI and AII were decreased compared with controls (66.9±20.4 vs 109±18.4 mg/ dl for AI and 13.6±6.2 vs 28.2±3.4 mg/dl, for AII) and B increased (121.7±21.7 vs 51.4±16.2 mg/ dl). Total cholesterol (C) was 6.51±1.76 vs 4.02±0.95 in controls, VLDL-C 1.56±0.88 vs 0.13±0.06, LDL-C 3.46±1.14 vs 2.50±0.63 and HDL-C 0.63±0.19 vs 1.37±0.30 mmol/l respectively. Total triglyceride (Tg) was 7.89±4.97 vs 0.95±0.33 and VLDL-Tg 3.93±2.68 vs 0.39±0.12 mmol/ l in controls. In CNF lipoprotein lipase activity (LPL) was reduced (9.94±6.3 vs 24.1±5.6 umol/ FFA/ml/h, p< 0.001), but hepatic lipase was normal (47.5 vs 50.4).

In conclusion: normal growth and development can be achieved during the first year of life in CNF infants with dietary manipulations but the patients may exhibit an increased risk for arteriosclerosis caused by an increase of C and Tg in lipoprotein fractions, low levels of HDL-C and it's apoproteins, and by low LPL activity.

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THE DISTRIBUTION OF ENDOGENOUS ALBUMIN IN THE GLOMERULAR WALL OF PROTEINURIC PATIENTS - AN IMMUNO ULTRASTRUCTURAL STUDY.

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Glomerular proteinuria seems related, in part, to loss or impairment of the normal barrier function of the glomerular capillary wall. Endogenous albumin was revealed in the glomerular wall of proteinuric patients and compared with a non-proteinuric control by immunoelectron microscopy using the protein A-gold method. In the control biopsy, peaks of albumin accumulation were noted in the subendothelial area and in the inner portion of the lamina densa, with gradual tapering of the distribution towards the epithelial side of the basement membrane. The urinary space and epithelial cells were unlabelled. In tissues from proteinuric patients, albumin was distributed throughout the entire width of the glomerular basement membrane, though the pattern of accumulation varied between patients. Mesangial areas were heavily labelled in tissues from both control and proteinuric patients. In the latter, lysozomes in tubular epithelial cells also accumulated albumin, evidence of reabsorption.

These results reveal the existence, in normal conditions, of a barrier located in the subendothelial area of the glomerular basement membrane, the loss of which, as in the idiopathic nephrotic syndrome, leads to diffuse distribution of albumin in the glomerular capillary wall. Supported by CAFIR, Univ. de Montreal (P.R.) and the MRC (M.G.).

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THE ROLE OF NEUTROPHILS IN THE PATHOGENESIS OF HAEMOLYTIC URAEMIC SYNDROME: MEASUREMENT OF FREE AND COMPLEXED ELASTASE. M M Fitzpatrick, V Shah, G Filler, M J Dillon, T M Barratt

There is evidence of involvement of polymorphoneutrophil leucocytes (PMNL) in the pathogenesis of the haemolytic uraemic syndrome (HUS). In diarrhoea associated (D+) HUS the PMNL count is raised and a high value predicts a poor outcome, but in D- HUS the PMNL count is normal. Elastase is a lysosomal proteinase liberated by activated PMNL and complexed in the circulation by α1-antitrypsin (α1-AT). We were unable to detect free elastase activity in the plasma of 20 children with D+ HUS using a specific substrate. We therefore developed an enzyme linked immunosorbent assay (ELISA) for measuring elastase bound to α1-AT in the plasma of normal children, those with D+ HUS, D- HUS, a high PMNL count for other reasons, and those with chronic renal failure (CRF).

		PMNL $x10^9$±SD	α1-AT Complexed Elastase µg/l geometric mean	range (±2SD)
Normals	n=35	6.0±1.2	0.29	0.11-0.76
D+ HUS	n=47	11.7±6.6	2.54*	0.62-10.5
D- HUS	n=9	5.1±1.9	1.13*	0.14-9.0
High PMNL	n=21	7.1±4.4	0.57	0.14-2.3
CRF	n=35		0.29	0.10-0.85

*$p<0.05$ vs controls

There was a significant positive correlation between α1-AT complexed elastase and PMNL count in both D+ HUS and controls, with the regression line significantly higher in the former.

The raised levels of α1-AT complexed elastase support the concept of PMNL activation in vivo with the release of neutrophil granule content in the acute phase of D+ HUS.

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IMMUNE RESPONSE TO STREPTOCOCCAL PROTEINASE IN ACUTE POST-STREPTOCOCCAL GLOMERULONEPHRITIS (APSGN)

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The glomerular basement membrane contains fixed negative charges, to which cationic antigens can bind inducing in situ immunecomplex formation and glomerulonephritis. Hemolytic streptococci secrete extracellular cationic proteins which could be identified in 8 out of 18 biopsy specimens from cases with APSGN. We investigated the antibody response to a prominent cationic extracellular product of streptococci called PROTEINASE (MW: 30 kD, pI: 8.4) and its precursor enzyme ZYMOGEN in 88 sera of 44 APSGN-patients and in 101 unselected sera of persons without glomerulonephritis using Westernblotting- and ELISA-techniques. The antibody-titers to Streptolysin O (ASLO), DNase B (ADNase B), Hyaluronidase (AHT) and Streptokinase (ASK) were also measured in all serum samples.
86.4% of the APSGN sera had anti-PROTEINASE-titers ≥ 1:3200, median 1:12800. In Westernblotting 93.2% revealed IgG- and 84% IgM-antibodies to PROTEINASE and/or ZYMOGEN. In respect to the traditional antibody-titers against streptococcal antigens the best correlation to APSGN was found with ADNase B, which was increased in 75%. AHT was elevated in 52.3%, ASLO in 43.2% and ASK in only 11.4%. The antibody response to PROTEINASE and ZYMOGEN of the control sera was significantly less than that of the APSGN sera even in the presence of elevated titers of traditional anti-streptococcal antibodies.
Our results suggest a role of cationic streptococcal PROTEINASE in the pathogenesis of APSGN.

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MODULATION OF MESANGIAL CELL ACTIVITY BY THE LECTINIC BINDING OF GLIADIN

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We previosly demonstrated the binding of gliadin, a gluten lectin fraction, to rat mesangial cells in culture. This reaction involves lectin binding sites on mesangial cell surface through glycosilated residues since it can be inhibited by competitive sugars.
Aim of this work was to obtain further insight into the possible functional effects induced by the binding of gliadin to cultured rat mesangial cells on the production of Prostaglandin E2 (PGE2).
Mesangial cells in culture were obtained from Sprague-Dawley rat glomeruli after treatment with collagenase and subsequent subcultures to eliminate the epithelial and endothelial components.
Pure mesangial cells obtained in 4th subculture were incubated in Ca++ and Mg++ Hank's salt solution for 60 minutes at 37°C in basal conditions, after stimulation with ionophore Ca++ 2 μM, in coincubation with gliadin 100 μg/ml with and without indomethacin 1 μM.
The measurement of PGE2 by competitive radio-immunoassay employing a specific monoclonal antibody showed mean levels of PGE2 in colture supernatant significantly reduced after incubation with gliadin in comparison to basal conditions (73.47±28.42 pg/μg protein vs 208.38±120.01 pg/μg protein, p<0.001).
The coincubation of gliadin with indomethacin significantly decreased the PGE2 production (48.92±33.48 pg/μg protein, p<0.01).
These data indicate that the binding of gliadin to mesangial cells can modulate their production of PGE2.

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INTESTINAL PERMEABILITY AND ANTIBODIES AGAINST DIETARY ANTIGENS IN IGA NEPHROPATHY

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Dietary antigens are thought to have a role in the pathogenesis of IgA Nephropathy (IgAN). Aim of this paper was to investigate the integrity of gut mucosal barrier and to evaluate the levels of circulating antibodies against dietary antigens in children with IgAN.
Intestinal permeability was measured in 14 children with IgAN and 15 age-matched controls. After an oral load of 2.5 g of Lactulose (LAC) and 0.5 g of Rhamnose (L-RH), percent of urinary recovery in the 5 hours urine collection was assessed by chromatography. IgG and IgA anti-gliadin, -βlactoglobulin, -αlactalbumin, -casein and ovalbumin antibody serum levels in 20 IgAN patients and 41 age-matched controls were measured by Elisa technique.
In IgAN children urinary LAC/L-RH ratio was higher than in controls ($p<0.05$). In IgAN patients IgG and IgA anti-casein and IgA anti-ovalbumin antibody serum levels were higher than in control group ($p<0.05$). There is no significant correlation between the high levels of serum antibodies and the increased urine LAC-L-RH ratio.
Our results indicate that an abnormal gut permeability and increased serum levels of antibodies against milk and egg proteins are present in IgAN. It remains to be established the role of this findings in the pathogenesis of IgAN.

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DISTINCTION BETWEEN GLOMERULAR AND NON-GLOMERULAR HAEMATURIA USING AUTOMATED RED CELL ANALYSIS

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Urinary red cells arising from glomeruli show deranged morphology when examined by phase contrast microscopy, whereas those arising from the lower renal tract do not. We aimed to show whether measurement of red cell indices using an automated counter could provide a more objective and simpler indication of the source of haematuria. In a double blind study fresh urine was obtained from 25 children with haematuria. Twelve had biopsy proven glomerular disease. 13 [the control group] had haematuria following urological surgery. After concentration by centrifugation the resuspended deposit was examined by phase contrast microscopy and analysed using a Technicon H1 system for erythrocyte indices. All the urine from the glomerular and one from the control groups showed more than 20% dysmorphic red cells by phase contrast microscopy [P<0.001]. Red cell indices showed a significantly lower mean corpuscular volume [P<0.005] and a higher red cell distribution width [SD of corpuscular volume/mean corpuscular volume] [P<0.02] in those patients with glomerular disease. We suggest that patients with a mean corpuscular volume of <70fl and a red cell distribution width of >22% should firstly be investigated as glomerular haematuria and vice-versa as non-glomerular haematuria. Phase contrast microscopy was the most specific but was time consuming and subject to inherent observer variation. The automated method provides an easy alternative.

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INTERSTITIAL RENAL INFLAMMATION WITH UVEITIS (IRI - U)

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(IRI - U) is a rare entity in children. There exists idiopathic forms with no apparent cause or association with known diseases. The aim of this study was to describe 5 new unpublished cases seen in our institution. The children were 4 boys and 1 girl 12 to 13 10/12 years old. The first symptoms were fatigue, prolonged fever, joint abdominal pains, diarrhea and polyuria. The uveitis occurred after the onset of the nephropathy. In all cases hyperglobulinaemia and high ESR were present : all children presented signs of proximal tubular dysfunction : glycosuria, proteinuria of tubular type, polyuria. A significant decrease of the glomerular filtration rate was noted in two children (creatinine clearance 20 and 30 ml/mn/1,73 m2).

No clinical, biological, radiological nor pathological sign of sarcoidosis, sjögren's syndrome, infection were found.
Renal biopsies were performed. In all cases, they showed infiltration in the interstitial tissue and in 3 cases a granuloma. There was no glomerular nor vascular lesions. Immunofluorescence studies revealed no deposits in the glomeruli, some fixation of C3 along tye tubular basement membrane, some IgA, IgG and IgM plasmocytes in the interstitial tissue.
Repeated biopsies have been performed in 3 children. They showed in all cases a significant improvement of the interstitial lesions.
All patients were treated with corticostéroïd. After a follow up ranging from 2 to 6 years the course of the disease was always benign.

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RENAL MULTICYSTIC LYMPHANGIECTASIA IN A 2 YEAR OLD GIRL

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A 2 year old girl born from healthy parents was admitted to our hospital with two enlarged kidneys, hypertension and polyuria. Positive physical findings were : high blood pressure (HBP) 140/110 mmHg, obvious enlarged kidneys and erythrosic face. Growth was normal, creatininemia 30 mol/l (clearance = 81 ml/mn/1,73 m2), maximum urine concentration low at 380 mOsm/l, without hematuria, albuminuria or glucosuria. Erythrosic face was due to polyerythrocytemia 6,9 x 10^9/l, hemoglobin : 17,8 g/100 ml and hematocrit 59 %. Echotomography confirmed enlarged kidney (95 and 105 mm) with a hypoechogenic border and a heterogenic and hyperechogenic parenchyma with little cystis. Scan tomography showed heterogenic parenchyma with multicystic cortex and a perirenal liquid effusion. Liquid aspiration was performed with a clear liquid (Na+ : 131 mmol/l, K+ : 4 mmol/l without albumin). Renal biopsy showed normal glomerulars and tubules in a parenchyma distorted by irregular enlarged cavities, lined by endothelial cells enmarked by epithelial markers. Electronic microscopic examination confirmed the endothelial border aspects of these cavities. Diagnosis was bilateral lymphangiectasia localised in the kidneys. HBP was controlled by enalapril (2,5 mg/kg/day) and polyerythrocytemia by regular bleeding. Dipyridamol (5 mg/kg/day) was given to avoid thrombosis.
Renal lymphangiectasia is very rare in adults and unknown in children. The relationship between renal abnormalities and the symptoms of this girl remains unclear. Etiology and prognosis of renal lymphangiectasia are unknown.

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RENAL INVOLVEMENT IN PROGRESSIVE IDIOPATHIC CHOLESTASIS (PIC OR BYLER'S DISEASE).

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PIC seems to be an heterogeneous group of intrahepatic cholestatic diseases of unknown origin, beginning during the first year of life and characterized by moderate cholestasis, severe pruritus, diarrhea with intestinal malabsorption and an evolution towards hepatic fibrosis. We report 2 cases, beginning at age 6 months (case 1) and 15 days (case 2) in whom PIC was associated with renal tubular dysfunction including glycosuria, low molecular weight proteinuria, generalized aminoaciduria, hypouricemia with high renal clearance, hypophosphatemia with low reabsorption rate and severe rickets, hypokaliemia, and moderate concentration defect. Patient 1 needed constant rate enteral nutrition. Rickets were healed by high doses of phosphorus and 1-25 $(OH)_2$ D_3. Hepatic transplantation was performed at age 4. Ten months later, tubular dysfunction persists less important. Patient 2 had a more severe presentation with severe digestive intolerance requiring total parenteral nutrition and, in addition to other tubular symptoms, deep acidosis, hypercalciuria and nephrocalcinosis. Indomethacin allowed a partial improvement of tubular disorders. The child died at age 10 months, from septicemia, marasmus and digestive bleeding. The main renal pathologic changes consisted in irregular, often flattened and spongy proximal tubular epithelium, and dilatation of distal tubular lumen around hyaline casts. Intestinal biopsy showed partial villous atrophy.
The association of hepatic, intestinal and tubular defects observed in these 2 children suggests a possible alteration of intracellular transport in PIC syndrome.

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