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36. This research was supported in part by United States Public Health Service Research Grant No. HD-08568 and by ALSAC.
37. We are indebted to Ms. E. Pell for technical assistance and to Mr. J. Gilbert for his expert assistance in the preparation of the manuscript.
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39. Accepted for publication November 10, 1975.

Pediat. Res. *10:* 197–201 (1976)

Kidney serum oncotic pressure
lipoid nephrosis sodium

A Study of the Renal Handling of Water in Lipoid Nephrosis

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Extract

Children with lipoid nephrosis were studied during clinical relapse and after complete remission. As expected, the calculated serum oncotic pressure was reduced severely from the remission value of 28.6 ± 0.9 mm Hg to 15.4 ± 1.1 ($P < 0.005$) during relapse. Although no apparent change in plasma volume was noted using the volume of distribution of labeled human albumin, calculated plasma volume was reduced 13 ± 8% during relapse when estimated from changes in hematocrit. After a water load, the ability to excrete water was markedly blunted during relapse. The clearance of solute-free water (C_{H_2O}) was 0.9 ± 0.8 ml/min during relapse, compared with 3.6 ± 0.6 ml/min during remission ($P < 0.005$). In addition, there was a reduced maximal urinary concentrating ability during relapse in four of the six patients examined. Mean urine osmolality for the group during relapse was 778 ± 82 mOsm/kgH_2O and 991 ± 71 during remission ($P < 0.05$).

The demonstrated alteration in nephron function during relapse of nephrotic syndrome could result from either (*1*) a decrease in the amount of sodium delivered to the ascending limb of the loop of Henle because of increased proximal reabsorption or (*2*) a change in the intrinsic characteristics for sodium reabsorption in that segment. Although this observation does not prove that proximal reabsorption is increased, it suggests a common underlying mechanism for altered nephron function in all of the major edema-forming conditions.

Speculation

The finding that C_{H_2O} and maximal concentrating ability are reduced during relapse of the nephrotic syndrome suggests that the reabsorption of sodium is increased in the proximal segment of the nephron. This process may explain the refractoriness to diuretic therapy encountered in some patients with nephrotic syndrome despite the presence of a normal glomerular filtration rate.

Previous clinical studies have demonstrated a markedly impaired water diuresis after water loads in both congestive heart

failure (2) and decompensated hepatic cirrhosis (14). This finding is thought to reflect increased reabsorption of sodium in the proximal portion of the nephron (18). Similar studies have not been performed in the nephrotic syndrome. It was of interest, therefore, to examine the capacity to excrete a water load in this condition to determine whether the same alteration in nephron function underlies all of the major clinical states characterized by edema formation, despite different primary causes.

Children with lipoid nephrosis were studied during clinical relapse and after complete remission. In this way, it was possible to examine functional parameters of the kidney when an inexorable retention of sodium was present as well as when renal tubular function was completely normal.

PATIENT MATERIAL AND METHODS

Six patients with lipoid nephrosis were studied on two occasions, during clinical relapse and after complete remission. All patients had the characteristic polyrelapsing, steroid-sensitive clincial course of lipoid nephrosis, and in two patients the typical histologic features of the disease by renal biopsy were present (19). Age of the patients at the time of study ranged between 5 and 21 11/12 years and averaged 12 3/12 years. All studies were performed in the Children's Clinical Research Center at Yale-New Haven Hospital. Possible hazards of the procedures were explained to both the patients and their parents, and informed consent was obtained before the study.

Patients were investigated for the first time 8–30 days after clinical evidence of relapse was present, *i.e.*, hypoalbuminemia, proteinuria, and edema. After the initial study, conventional prednisone treatment was begun in a dose of 2 mg/kg/24 hr. Complete clinical remission was defined as a lack of proteinuria, loss of edema formation, and a normal serum albumin. Patients were studied a second time 37–116 days later when a complete remission had been sustained and after all treatment was discontinued for at least 4 weeks. During each study period the following determinations were made.

FIRST DAY

A complete physical examination was performed and the following tests were performed: hematocrit, hemoglobulin, white blood cell count, urine analysis, quantitative 24-hr urine protein, serum protein by the biuret method with albumin and globulin fractionation, serum electrolytes, blood urea nitrogen, serum creatinine by Jaffe method, and blood glucose. Urine glucose was estimated by an enzymatic method (23) and was negative in all cases.

Total plasma volume was calculated from the volume of distribution of radioactively labeled human serum albumin (21). Stock solutions containing 1.0 g protein/100 ml were diluted with acid-citrate-dextrose solution to a concentration of 10 μCi/ml. One milliliter of the final solution containing approximately 1 mg protein was administered intravenously. Samples of blood were obtained from an antecubital vein in the opposite upper extremity at 5 and 10 min, and the volume of distribution at zero time was estimated. Aliquots of blood for determining the specific activity of radioiodine and hematocrit were obtained from a free-flowing venous puncture with the patient kept supine before and during plasma volume measurement. In order to reduce thyroidal uptake of radioiodine, potassium iodide in a dose of 300 mg/24 hr was administered 24 hr before and 48 hr after the plasma volume determination.

In addition, since there was no change in red cell indices during relapse and remission, changes in plasma volume could be estimated from the hematocrit values $(Hct_1 - Hct_2 \cdot 100)/Hct_2$, where Hct_2 was the value during remission and Hct_1 was the value during relapse.

SECOND DAY

Maximal urinary concentration (U_{max}) was determined using the method of Miller (16). Fluid was withheld beginning at 8:30 PM; 12 hr later urine samples were collected each hour for osmolality until values changed by less than 30 mOsm/kg H_2O when urine osmolality was stable; aqueous vasopressin (2.5 or 5.0 U) was given subcutaneously. Urine osmolality was determined 1 hr later.

THIRD DAY

A water load was administered as 20 ml/kg *per os* over a 120-min interval between 8:00 and 10:00 AM. Water intake was maintained throughout the remainder of the test to match the measured urine volume. Inulin and *p*-aminohippurate (PAH) clearances were measured with a primary and sustaining dose in 5% glucose-water calculated to produce plasma levels of 20 mg/100 ml and 1–3 mg/100 ml, respectively, at an infusion rate of 1 ml/m^2 body surface area. After a 45-min period for equilibration, three or four urine collections of 30 min each were collected. The plasma concentration of inulin and *p*-aminohippurate were determined from blood samples taken at the midpoint of each urine collection. Patients were encouraged to void spontaneously and completely for each collection.

Conventional formulas were used to calculate inulin clearance (C_{in}) and *p*-aminohippurate clearance (C_{PAH}). Free water clearance was calcuated as $V - C_{osm}$. Delivery of sodium to the early portion of the distal tubule was estimated from the expression $C_{H_2O} + C_{Na}$, as suggested by Barton *et al.* (1).

Colloid oncotic pressure was calcuated from the formula: $2.8\ c + 0.18\ c^2 + 0.012\ c^3$, where c equals total protein in grams per 100 ml (15).

Determination of the inulin concentration in plasma and urine samples was made using the anthrone method by a technique adapted for the AutoAnalyzer method (5) and PAH by the method of Smith and associates (8). Urine and plasma osmolalities were performed on an Advanced Instruments osmometer and sodium concentration on a flame photometer with an internal standard.

A paired *t*-test was used to compare changes in relapse and in remission. Values given are means ± SEM.

RESULTS

Results of plasma volume determinations and studies performed during water loading are shown in Table 1. As expected, the calcualted oncotic pressure was severely reduced from the remission value of 28.6 ± 0.9 mm Hg to 15.4 ± 1.1 ($P < 0.005$) during relapse. To determine changes on plasma volume in association with relapse of the nephrotic syndrome, two methods were used to estimate the value. Although no apparent change in plasma volume was noted using the volume of distribution of labeled human albumin, plasma volume was reduced 13 ± 8% during relapse when estimated from changes in hematocrit.

Since each patient served as his own control, the values derived from clearance studies are expressed in absolute units rather than as a function of surface area or body weight. As shown in Table 1, mean glomerular filtration rate (C_{in}), effective renal plasma flow (C_{PAH}), and filtration fraction (C_{in}/C_{PAH}) were similar during both periods of study for the group (*P*, not significant) Glomerular filtration rate, however, was markedly reduced in two cases (*KH* and *TM*) during relapse and, in one case (*RH*), slightly reduced during chronic remission.

After a water load, the ability to excrete water was markedly blunted during relapse. Urine flow rate averaged 3.0 ± 1.1 ml/min during relapse compared with 5.5 ± 0.8 during remission ($P < 0.05$). Although four of the six patients achieved a hypotonic urine in relapse, the average urine osmolality (330 ± 108 mOsm/kg H_2O) was significantly higher than the remission value of 114 ± 12 ($0.01 < P < 0.05$). In addition, the C_{H_2O} was reduced during relapse, 0.9 ± 0.8 ml/min, compared with 3.6 ± 0.6 ml/min during remission ($0.001 < P < 0.005$). Since urine remained hypertonic to plasma in two cases in whom partial release of vasopressin may have persisted C_{H_2O} was also compared with the four subjects who achieved a hypotenic urine on both occasions. When

Table 1. *Plasma volume and renal function[1] during water loading*

Subject	Plasma volume, [^{135}I]albumin	Hct, %	C_{in}, ml/min	C_{PAH}, ml/min	C_{in}/C_{PAH}	V, ml/min	P_{osm}, mOsm/kg H_2O	U_{osm}, mOsm/kg H_2O	C_{H_2O} ml/min	C_{H_2O} ml/min/100 ml GFR	$C_{Na}+C_{H_2O}$ ml/min	$C_{Na}+C_{H_2O}$ ml/min/100 ml GFR
KH												
Relapse	1.120	44	31	420	0.10	1.0	270	136	0.5	1.6	0.5	1.6
Remission	1,170	30	126	240	0.53	4.2	286	95	3.0	2.4	3.5	2.8
RH												
Relapse	1,420	35	73	281	0.25	3.2	287	195	0.2	0.3	0.9	1.2
Remission	1,620	37	53	381	0.14	2.7	288	119	1.6	3.1	1.9	3.6
LD												
Relapse	3,100	42	115	832	0.14	5.8	285	169	2.4	2.1	4.2	3.7
Remission	2,400	40	112	360	0.31	5.9	278	123	3.4	3.0	4.7	4.2
DB												
Relpase	2,400	47	111	559	0.20	1.0	283	652	(−) 1.0	(−) 0.9	(−) 0.7	(−) 0.6
Remission	4,800	40	112	685	0.16	6.2	279	166	3.5	3.0	4.6	4.1
SC												
Relapse	2,050	44	125	461	0.27	6.5	289	142	3.8	3.0	4.6	3.7
Remission	1,770	41	93	510	0.18	8.3	287	88	5.8	5.2	6.6	7.1
TMc												
Relapse	1,080	46	56	264	0.21	0.4	262	688	(−) 0.6	(−) 1.2	(−) 0.6	(−) 1.1
Remission	1,120	42	92	424	0.26	5.9	285	95	4.2	4.6	4.7	5.1
P value[2]	NS	<0.05	NS	NS	NS	<0.05	NS	<0.05	<0.05	<0.01	<0.01	<0.01

[1] Average values from three to four clearance periods are represented. Hct: hematocrit; GFR: glomerular filtration rate.

[2] *P* value represents comparison of relapse period to that of remission. NS: not significant.

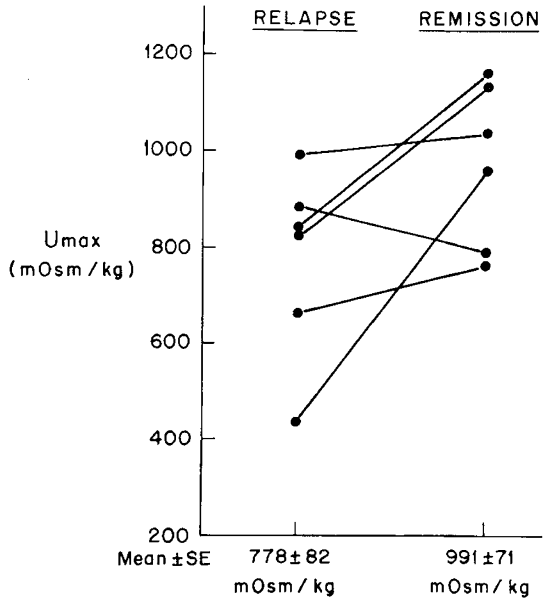

Fig. 1. Maximal renal concentrating ability (*Umax*) in patients with lipoid nephrosis during relapse and while in remission.

examined in this way, C_{H_2O} remained significantly decreased during relapse, 1.7 ± 0.8 ml/min, compared with remission (3.4 ± 0.8). Moreover, comparison of C_{H_2O}/100 ml glomerular filtration rate (GFR) for the group as a whole or the four cases with hypotonic urine also demonstrated a significant reduction during the period of clinical relapse. In addition, delivery of sodium to the distal tubule, estimated from (C_{H_2O} + C_{Na})/100 ml GFR (1), was markedly decreased in children during relapse of the nephrotic syndrome. The (C_{H_2O} + C_{Na})/100 ml GFR was 1.6 ± 0.8 ml/min during relapse and 4.5 ± 0.6 during remission ($0.005 < P < 0.01$).

In studies performed to determine urine-concentrating ability there was a progressive increase in urine concentration during both study periods with continued dehydration. Urine osmolality reached a plateau, with an hourly variation of 30 mOsm/kg H_2O or less, in 17.4 ± 0.8 hr during relapse and in 16.1 ± 1.0 hr during remission (P = not significant (NS)). At that time there was no difference in plasma osmolality, which averaged 287 ± 3.2 mOsm/kg H_2O in the experimental period and 289 ± 2.0 in the control study (P = NS).

As shown in Figure 1, there was a reduced maximal urinary concentrating ability during relapse in four of the six patients examined. Mean urine osmolality for the group during relapse was 778 ± 82 mOsm/kg H_2O and 991 ± 72 during remission ($0.01 < P < 0.05$). There was no evidence of a defect in antidiuretic hormone production during relapse to account for the reduced concentrating ability. After the administration of aqueous vasopressin, urine osmolality changed further by only 6.3% in the relapse study and by 4.18% during remission. Miller (16) has demonstrated that in patients with partial ADH insufficiency there is a further increase in urine osmolality of 9–67% after injection of vasopressin.

DISCUSSION

It is well established that a major process mediating the concentration and dilution of urine is the reabsorption of sodium in the ascending limb of the loop of Henle, which is the water-impermeable segment of the nephron. Since the capacity to reabsorb sodium in this segment is thought to be unsaturable, measurement of C_{H_2O} and the reabsorption of solute-free water ($T^c_{H_2O}$) have been used as indices of sodium reabsorption in the proximal segment of the nephron (7, 18). An increase in proximal reabsorption would result in a decrease in the amount of sodium delivered to the ascending limb and, consequently, would be reflected by a decrease in these parameters of renal function which are dependent upon sodium absorption at that site. Previous studies in man have suggested enhanced proximal reabsorption in congestive heart failure, cirrhosis of the liver, and adrenal insufficiency. In each of these conditions, the ability to generate free water (C_{H_2O}) and excrete a water load (2, 14, 18) and/or the ability to reabsorb solute-free water ($T^c_{H_2O}$) and produced a concentrated urine (22) is impaired. In these reports, experimental groups of patients were

compared with normal subjects because of the chronic nature of the pathologic condition.

In the present study, the capacity to excrete a water load was examined in a group of children with an edema-forming condition. Since lipoid nephrosis is a reversible condition, each child could serve as his own control by being studied during complete remission, as well as during relapse. Since glucocorticoid therapy has been reported to influence water permeability of renal tubules (6), clearance studies were performed before instituting therapy and when patients had been off therapy for a minimum of 4 weeks, in remission.

The present study demonstrates an impairment in the ability to excrete free water during clinical relapse of the nephrotic syndrome. In response to a similar water load, the volume of urine excreted during relapse was approximately one-half of the value observed during remission, and there was a marked difference in the clearance of solute-free water when measurments of C_{H_2O} during relapse were compared with the period of remission. The difference in C_{H_2O} remained significant even when *patients DB* and *TM*, in whom urine remained hypertonic to plasma during relapse, were excluded and when C_{H_2O} was fractored by GFR. In addition, an impairment in maximum urinary concentrating ability was demonstrated during clinical relapse in four of the patients.

The demonstrated alteration in nephron function during relapse of nephrotic syndrome could result from either (*1*) a decrease in the amount of sodium delivered to the ascending limb because of increased proximal reabsorption, (*2*), a change in the intrinsic characteristics of tubular sodium reabsorption, or (*3*) changes in medullary blood flow. Several observations, in addition to the present data, support the first possibility. Increased proximal sodium reabsorption has been demonstrated in congestive heart failure (2) and decompensated liver disease (18) when associated with significant edema formation. In both conditions, clearance studies have demonstrated a reduction in C_{H_2O} and $T^c_{H_2O}$ when compared with values for normal subjects under conditions of similar urine flow rate and C_{Osm}. In addition, the infusion of a poorly reabsorbable solute such as mannitol or volume expansion with albumin, experimental manipulations designed to reduce proximal reabsorption, resulted in increased sodium and free water excretion and, therefore, suggested increased delivery of sodium to distal sites (18). Although increased secretion or decreased catabolism of antidiuretic hormone could have resulted in the observed defects in C_{H_2O}, this seems unlikely since the defect persisted during infusion of ethyl alcohol, and the data suggest normal rates of hormone inactivation (18). Similarly, the marked reduction in the ability to excrete free water and the decreased delivery of sodium to the distal tubule demonstrated in the present study would suggest that increased proximal reabsorption may occur during relapse of the nephrotic syndrome.

Using the technique of distal tubular blockade, Grausz and associates (9) have suggested recently that sodium retention in nephrotic syndrome occurs because of excessive distal reabsorption. This conclusion was based on the assumption that changes in electrolyte excretion after the administration of chlorothiazide and ethacrynic acid reflect only alterations in sodium reabsorption in the distal nephron. Numerous micropuncture studies, however, have shown that ethacrynic acid has a marked inhibitory effect on proximal, as well as distal, reabsorption (4). Ethacrynic acid also produces significant renal hemodynamic changes which may influence electrolyte transport (3). Moreover, since the fractional excretion of sodium rose 40% or more in Grausz's studies, it is possible that volume expansion resulted from efforts to balance the extremely high rates of urine flow. Consequently, these considerations make the interpretation of Grausz's findings complicated, and a comparison with our patients who were studied in a nondiuretic state is difficult.

Changes in medullary blood flow would be expected to alter the medullary osmolar gradient, and, therefore, impairment of concentrating ability may not reflect changes in sodium reabsorption in the ascending limb. Although the distribution of intrarenal blood flow has not been examined in patients with nephrotic syndrome, an increase in deep cortical and meduallary flow might be expected since such a pattern has been found in several conditions characterized by excessive sodium retention, including heart failure (13), hepatorenal syndrome (11), and thoracic vena caval occlusion (12). Although this mechanism cannot be excluded and could contribute to the concentrating defect during relapse, it seems unlikely that an increased medullary blood flow would influence the diluting segment located principally in the cortical zone. Moreover, a reduction in medullary solutes during relapse of the nephrotic syndrome would reduce back diffusion of water in collecting ducts and, consequently, enhance both V and C_{H_2O}. However, both V and C_{H_2O} were diminished during relapse in our patients.

In an elegant reveiw of the possible mechanisms for edema formation in 1948, Peters (17) suggested that a reduction in blood or plasma volume could result in an increase in salt retention in an effort to conserve water, even in edema-forming states. This hypothesis remains unproven today, as in 1948, because of the lack of an accurate method to measure effective or circulatory plasma volume. In the present study and in previous studies (10), no definite change in plasma volume was found when estimated from substances which bind to albumin. However, plasma volume, when estimated from hematocrit values, was decreased during relapse.

Several important facts concerning the care of patients with the nephrotic syndrome as well as renal sodium handling are illustrated by these studies. First, in the nephrotic syndrome, like congestive heart failure and decompensated cirrhosis, the ability to excrete water during water loading is reduced. Although this observation does not prove that proximal reabsorption is increased, it suggests a common underlying mechanism for abnormal nephron function in the major edema-forming conditions. Second, impairment of free water clearance provides an explanation for the tendency towards hyponatremia in some patients during relapse of nephrotic syndrome. Third, since the principal site of action of most potent natriuretic agents is in the ascending limb, reduced sodium reabsorption in that segment of the nephron may explain the refractoriness to conventional diuretic therapy so often encountered in this group of patients despite the presence of a normal filtration rate (20).

SUMMARY

Children with lipoid nephrosis were studied during relapse and after complete remission of the nephrotic syndrome. The ability to excrete a water load was markedly blunted during relapse. In addition, C_{H_2O} was 3.0 ± 1.1 ml/min during relapse compared with 5.5 ± 0.8 during remission. Studies performed to determine maximal urine-concentrating ability demonstrated reduced concentration during relapse in four of six patients. These data suggest increased proximal tubular reabsorption of sodium during relapse of nephrotic syndrome.

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25. Dr. Hayslett is an Established Investigator of the American Heart Association.
26. This study was supported by United States Public Health Service Grants nos. TIAM 5015 and AM 18061 and by the American Heart Association.
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29. Accepted for publication November 10, 1975.

Pediat. Res. *10:* 201–204 (1976)

American Pediatric Society Presidential Address

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This Society was founded 85 years ago with the goal of improving the health and well being of children. Over the years members of our society have indeed contributed in a great many ways to the improvement of life expectancy and of the general health of children.

For example, members of the American Pediatric Society showed that gastroenteritis causes death by inducing serious derangements of body fluids and electrolytes. The monumental work of James Gamble, Daniel Darrow, Alan Butler, Oscar Schloss, and their colleagues brought about an immediate decrease in the case fatality rate of infantile diarrhea. These great pediatricians applied the expanding knowledge of biochemistry to the solution of one of the most dangerous diseases of infancy. Their work represents one of the very best examples of the prompt application of newly discovered laboratory knowledge to the solution of a clinical problem.

No one who attended the meetings of our society in the 1930's will ever forget the great electrolyte debates. Both intense heat and brilliant light were generated by the debaters. The spectators were warmed, dazzled, and inspired.

It is interesting that the improvement in the treatment of gastroenteritis was accomplished without a clear understanding of the etiologic agents involved. This situation is, of course, not a rare one in medicine. By the end of the 1930's the possible role of *Escherichia coli* in gastroenteritis had been studied by only one or two workers. There was no knowledge that bacterial enterotoxins are responsible for the loss of water and electrolytes from the intestine.

The idea that viruses might cause gastroenteritis was not seriously considered until the end of the 1930's. In 1938 Reimann attempted to transmit gastroenteritis by fecal filtrates fed to volunteers. The experiments were inconclusive.

In Baltimore in 1941, Dr. Jacob Light and I undertook a systematic search for diarrhea-producing viruses. We studied a number of outbreaks of diarrhea among infants in hospital nurseries. We failed to isolate a virus, although we used a variety of animals, including ferrets, rats, and mice. We also employed tissues from embryonic mice and embryonated hen's and duck's eggs, but to no avail.

However, in March 1942 we did isolate a Seitz-filterable agent from newborn infants ill with diarrhea. This agent regularly produced diarrhea in young calves, and we found it to be present in the stools of all affected calves. The infectious agent was passaged by nasal and oral inoculation 29 times in succession. Nine of these successive passages were carried out by Seitz-filtered, bacteria-free stool suspensions. In July of 1942 by using the calf as the experimental animal, an identical agent was obtained from infants involved in a second outbreak of diarrhea in a Baltimore hospital nursery. A third and a fourth sample of the same agent were obtained in August and in December of 1942 from sick infants in a nursery in a Washington hospital.

The size of the filterable agents was between 40 and 80 nm in