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Effect of plasma albumin on sodium reabsorption in patients with nephrotic syndrome

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Effect of plasma albumin on sodium reabsorption in patients with nephrotic syndrome. The effects of plasma albumin on renal tubular sodium reabsorption were studied in patients with the nephrotic syndrome who had severe hypoalbuminemia and edema. The technique of distal tubular blockade by chlorothiazide and ethacrynic acid with replacement of urinary losses was used to assess sodium reabsorption. "Proximal" tubular fractional reabsorption was distinctly lower than has been reported in normal individuals and in patients with cirrhosis and ascites studied under similar conditions. This finding suggests that hypoalbuminemia in man decreases fractional sodium reabsorption in the proximal tubules as has been demonstrated in laboratory animals. This conclusion was strengthened by demonstrating increased fractional and absolute sodium reabsorption when concentrated albumin was infused in the presence of the diuretic agents. Volume expansion with an iso-oncotic electrolyte solution resulted in a further decrease in "proximal" tubular fractional sodium reabsorption, usually in association with increased GFR. The data suggest that sodium retention and edema formation in patients with the nephrotic syndrome and hypoalbuminemia occurs despite depressed proximal tubular fractional reabsorption and therefore may involve reabsorption of an excessively large fraction of filtered sodium in distal portions of the nephron, primarily at sites where ethacrynic acid blocks sodium reabsorption.

Effet de l'albumine du plasma sur la réabsorption du sodium chez les malades à syndrome néphrotique. Les effets de l'albumine du plasma sur la réabsorption du sodium par le tube rénal ont été éxaminés chez des malades nephrotiques, œdémateux et sévérement hypoalbuminémiques. La technique de blocage du tube distal par le chlorothiazide et l'acide éthacrynique, avec remplacement des pertes urinaires, a été employée pour évaluer la réabsorption du sodium. La fraction réabsorbée par le tube «proximal» était clairement plus faible que celle rapportée pour des individus normaux et des malades cirrhotiques et ascitiques éxaminés dans des conditions semblables. Cette observation suggère que l'hypoalbuminémie chez l'homme diminue la réabsorption du sodium par les tubes proximaux comme cela a été démontré chez l'animal de laboratoire. Cette conclusion était renforcée par la démonstration d'une augmentation fractionelle et absolue de la réabsorption du sodium, observée aprés l'infusion d'une solution concentrée d'albumine administrée en présence des agents diurétiques. L'éxpansion du volume extracellulaire à l'aide d'une solution électrolytique iso-oncotique éxagérait la diminution de la réabsorption fractionelle du sodium par le tube proximal associée, en général, avec une augmentation de la filtration glomérulaire. Ces résultats suggèrent que la retention sodée et la formation des œdèmes chez les malades néphrotiques et hypoalbuminémiques survient en dépit d'une dépression de la fraction réabsorbée par le tube proximal, et semble donc impliquer, pour les parties distales du nephron, une réabsorption fractionelle éxagérée de la quantité du sodium filtré prenant place, principalement, aux niveaux de blocage de la réabsorption sodée par l'acide éthacrynique.

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Pathways resulting in sodium retention in diseases characterized by edema formation are only partially understood. Recent studies in animals indicate that the natriuretic response following an infusion of saline involves decreased proximal tubular sodium reabsorption independent of aldosterone or glomerular filtration rate [1, 2]. It has been assumed generally that this decreased proximal tubular reabsorption is necessary for increased excretion of sodium during salt loading. Conversely, failure to decrease proximal tubular reabsorption could account for sodium retention in disease states. However, an important role of distal tubular reabsorption in the normal regulation of sodium excretion and in the pathophysiology of sodium retention has not been eliminated.

The commonly used diuretic agents chlorothiazide and ethacrynic acid appear to interfere with tubular sodium reabsorption extensively and predominantly in distal portions of the nephron [3–6]. Therefore, if the regulation of sodium excretion in man involves changes in proximal tubular reabsorption it would be expected that the state of sodium balance would influence the response to these diuretic agents [7]. In keeping with

this expectation we have reported an enhanced natriuretic effect of these diuretics in normal humans during salt loading (which would be expected to depress proximal tubular reabsorption), and a decreased natriuretic response in patients with cirrhosis and sodium retention [7], a situation which would be expected on theoretical grounds to be associated with increased proximal tubular reabsorption.

Patients with the nephrotic syndrome and hypoalbuminemia present an interesting theoretical inconsistency. On the basis of studies in animals it would be expected that hypoalbuminemia and decreased plasma protein osmotic pressure would lead to decreased proximal tubular reabsorption and natriuresis [8–11], yet patients with the nephrotic syndrome usually retain sodium avidly. If proximal tubular reabsorption is decreased in these patients as a result of hypoalbuminemia then the retention of sodium must relate to augmented distal tubular reabsorption. If so, patients with the nephrotic syndrome should demonstrate an exaggerated natriuretic response to the diuretic agents chlorothiazinde and ethacrynic acid which block sodium reabsorption in the distal nephron [3–6].

Methods

Five patients with the nephrotic syndrome were selected for study. Based on light and electron microscopy and immunofluorescent studies, two had "lipoid nephrosis", two had membranous glomerulonephritis and one had membranoproliferative glomerulonephritis. Prior to study each patient demonstrated stable values for GFR (creatinine clearance) and positive sodium balance while on an intake of approximately 50 mEq of sodium daily. Plasma albumin concentrations ranged from 1.0 to 1.9 g/100 ml and 24 hour urinary protein excretion ranged from 6 to 16 g. Studies were carried out on the General Clinical Research Center Metabolic Ward, and each patient gave informed consent after having been apprised of the experimental nature and possible hazards of the study.

After beginning a constant infusion of inulin and para-amino-hipputate (PAH) in 5% dextrose, the patients were hydrated by ingesting 1000 or 1500 ml of tap water over a 60 to 90 min period. Two hours later 3 to 5 control clearance periods were collected and then 250 mg of chlorothiazide was injected intravenously and added to the maintenance infusion to deliver 5 mg/min. Collections were continued for an additional 4 to 6 clearance periods after which 50 mg of ethacrynic acid was injected intravenously and added to the maintenance infusion to deliver 1 mg/min. Collections in the presence of the two diuretic agents were continued for 5 to 10 periods at the end of which time volume expansion was produced by infusing a solution containing Na 140, K 4.0, Cl 119 and lactate or bicarbonate 25 mEq/liter, and human serum albumin at the concentration equal to the patient's previously determined concentration of albumin in plasma. This solution was infused at a rate of 40 to 50 ml/min until a total of 1200 to 1800 ml had been infused. After completing this infusion collections were continued for 6 to 10 periods. The patient then received an intravenous infusion of 100 to 200 ml of 25% salt poor human albumin at a rate of 5 ml/min, during which time an additional 4 to 7 collections were made. After injecting chlorothiazide, and throughout the remainder of the study, urine volume was replaced quantitatively and independent of the loading solutions by infusing a solution containing Na 140, K 10, Cl 125, and HCO_3 25 mEq/liter. Collections of urine were made through an indwelling urinary catheter and samples of venous blood were collected during alternate clearance periods through an indwelling intravenous catheter placed in a superficial arm vein. Clearance periods were either 5 or 10 minutes in duration, depending on the rate of urine flow.

Plasma and urine were analyzed for inulin, PAH, Na, K, total protein and osmolality by methods decribed previously [12]. Urinary protein was precipitated with trichloroacetic acid prior to measuring inulin and para-aminohipputate. Albumin concentration in plasma was calculated from the electrophoretic pattern and the concentration of total protein determined by a biuret method.

Filtered sodium (F_{Na}) was calculated as GFR (clearance of inulin) × concentration of sodium in plasma (P_{Na}). The absolute rate of sodium reabsorption (T_{Na}) was calculated as the difference between F_{Na} and the sum of sodium and potassium excretion $(U_{Na}+U_K)V$[1]. The fraction of filtered sodium re-

[1] Although there is probably no 1:1 exchange of reabsorbed sodium for secreted potassium in the distal tubule, urinary potassium is the result of "secretion" beyond the proximal tubule [13]. Since proximal tubular reabsorption is isotonic and since the diuretic agents in combination virtually eliminate urinary diluting and concentrating ability, the addition of potassium to distal tubular fluid (and urine) should reflect at least an equivalent amount of sodium reabsorbed beyond the proximal tubule. Sodium reabsorption beyond the proximal tubule may be greater, but probably not less, than the amount of potassium added to "distal" tubular fluid if isotonicity is maintained throughout the nephron under conditions of these experiments. Therefore, this calculation should represent an approximation of the rate of sodium reabsorption proximal to the potassium "secretory" sites.

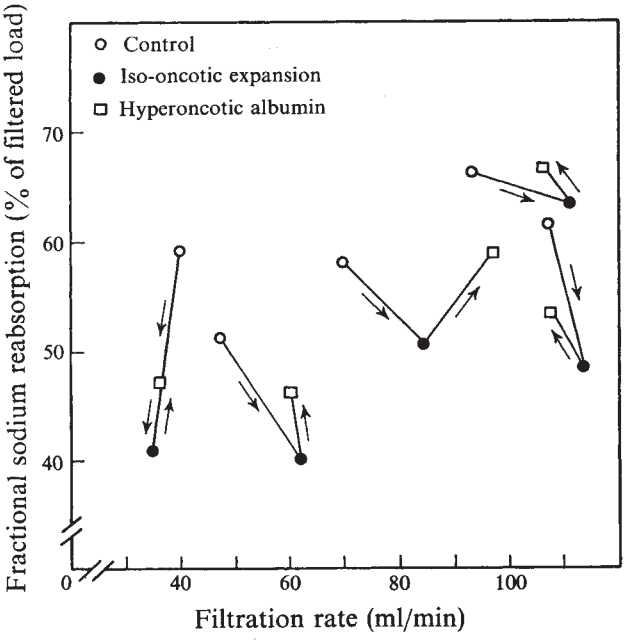

Fig. 1. *Relationship between fractional sodium reabsorption in the proximal tubule and filtration rate before and during iso-oncotic volume expansion and after infusing 25 g/100 ml albumin.* Points are the means of the last 3 to 6 consecutive clearance periods during each condition and the lines connect individual patients. Control collections were made during infusion of chlorothiazide and ethacrynic acid with quantitative replacement of urinary losses. These collections were followed by the infusion of an iso-oncotic modified Ringer's solution after which concentrated human serum albumin was infused.

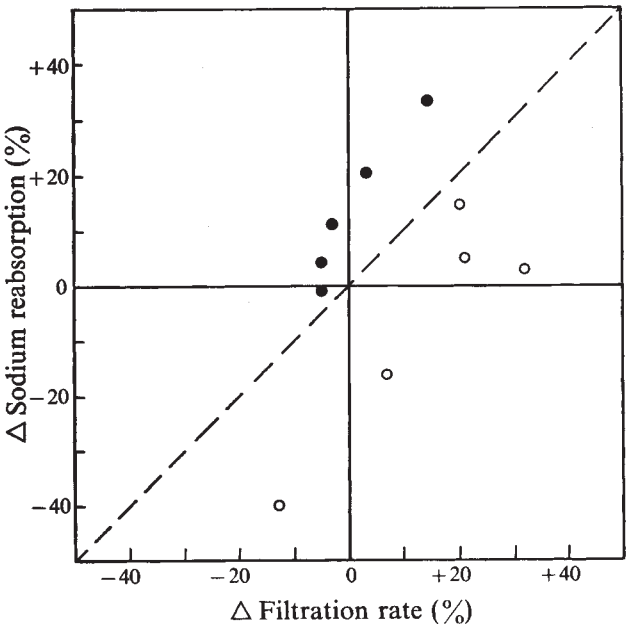

Fig. 2. *Changes in filtration rate and the absolute rate of "proximal" tubular reabsorption during iso-oncotic volume expansion and during infusion of concentrated albumin in the presence of distal tubular blockade in patients with nephrotic syndrome and hypoalbuminemia.* Each point is the mean of the last 3 to 6 consecutive collections under each condition in the 5 patients. Open circles represent the changes (from distal tubular blockade alone) produced by volume expansion with an iso-oncotic Ringer's solution. Solid points represent changes when albumin (25 g/100 ml) was infused after volume expansion. The broken diagonal represents unchanged fractional reabsorption; points above the diagonal indicate increased fractional reabsorption and points below indicate decreased fractional reabsorption. The upper half of the figure represents an increased absolute rate of tubular reabsorption and the lower half a decreased absolute rate of tubular reabsorption.

absorbed (FxT_{Na}) was calculated from F_{Na} and $U_{Na}+U_K$:

$$FxT_{Na}=1-\frac{(U_{Na}+U_K)\,V}{F_{Na}}.$$

Results

Fractional sodium reabsorption. The effects of chlorothiazide and ethacrynic acid on electrolyte excretion and tubular reabsorption are shown in Table 1. On the average chlorothiazide alone blocked the reabsorption of 5.3% of the filtered sodium. During the steady state effect of both chlorothiazide and ethacrynic acid the fraction of filtered sodium reabsorbed averaged 59.4 ± SD 5.5%. This represented an additional effect of ethacrynic acid to block reabsorption of 34.4% of the filtered sodium. The fraction of filtered sodium reabsorbed in these patients in the presence of both diuretic agents was distinctly lower ($P<0.01$)[2] than the average value of 68.7% previously found in a group of normal volunteers studied under similar conditions [7].

After infusing 1,200 to 1,800 ml of the iso-oncotic modified Ringer's solution, GFR increased in four out of five patients and the excretion of sodium and potassium increased in every patient. The fraction of filtered sodium reabsorbed decreased in every patient (Fig. 1) and fell to an average value of 48.7 ± SD 9.5%. These data from individual patients are summarized in Table 1. There was no consistent relationship between the extent of the decrease in fractional sodium reabsorption and the associated changes in filtration rate (Figs. 1 and 2, Table 1). The average fall in fractional sodium reabsorption of 10.7% after volume expansion was highly significant ($P<0.005$)[3].

After infusing 25 or 50 g of 25% human albumin GFR changed little (Figs. 1 and 2, Table 1), but the

[2] Based on Student's test for unpaired data.

[3] Based on Student's t test for paired data.

Table 1

Summary of effects of diuretic distal tubular blockade, acute iso-oncotic volume expansion and infusion of concentrated albumin in patients with the nephrotic syndrome[a]

Subject	GFR *ml/min*	C_{PAH} *ml/min*	FF	$U_{Na}V$ *μEq/min*	U_KV *μEq/min*	U/P_{Osm}	T_{Na} *mEq/min*	FxT_{Na} × 100	P_{Alb} *g/100 ml*
E. K.									
Control	36	407	0.09	8	5	0.99	4.92	99.7	1.0
CTZ	54	592	0.09	253	140	0.84	6.90	94.4	1.2
CTZ + EA	47	433	0.11	2882	177	0.97	3.29	51.3	1.6
Vol. Exp.	62	453	0.14	4997	271	0.92	3.29	40.1	1.4
Conc. Alb.	60	345	0.17	4142	255	0.89	3.82	46.1	1.9
D. R.									
Control	81	925	0.09	38	33	2.43	10.54	99.4	1.5
CTZ	84	859	0.10	592	77	0.84	10.59	94.1	1.3
CTZ + EA	93	1040	0.09	3976	237	1.02	8.34	66.5	1.2
Vol. Exp.	112	1301	0.09	5213	361	0.92	9.88	63.5	1.5
Conc. Alb.	106	1420	0.07	4412	434	0.90	9.68	66.7	2.7
M. L.									
Control	88	406	0.22	20	38	0.60	12.17	99.5	1.5
CTZ	92	502	0.18	769	135	0.80	11.88	92.9	1.7
CTZ + EA	107	477	0.22	5369	322	1.00	9.50	61.6	1.2
Vol. Exp.	114	624	0.18	8103	455	1.00	7.86	48.3	1.7
Conc. Alb.	108	663	0.16	7168	448	0.99	8.37	53.2	2.3
G. W.									
Control	23	132	0.17	2	41	0.50	3.04	98.6	1.7
CTZ	33	207	0.16	46	214	0.89	4.23	94.0	1.8
CTZ + EA	40	216	0.19	1831	386	0.97	3.18	59.1	1.6
Vol. Exp.	35	222	0.16	2369	432	0.91	1.99	40.7	1.6
Conc. Alb.	36	180	0.20	2197	444	0.88	2.40	47.3	2.9
K. W.									
Control	77	750	0.10	76	120	0.28	10.43	98.3	1.9
CTZ	79	723	0.11	501	282	0.50	10.04	93.4	1.8
CTZ + EA	70	756	0.09	3704	306	0.96	5.58	58.3	1.9
Vol. Exp.	85	1066	0.08	5500	352	0.95	6.05	50.7	2.6
Conc. Alb.	97	1109	0.09	5254	405	0.92	7.92	59.0	3.5
Means ± SD, $N = 5$									
Control	61	524	0.13	29	47	0.96	8.22	99.1	1.5
	±29	±314	±0.06	30	±43	±0.86	±3.99	±0.6	±0.1
CTZ	68	576	0.13	432	170	0.77	8.73	93.8	1.6
	±25	±247	±0.04	±285	±79	±0.15	±3.11	±0.6	±0.3
CTZ + EA	71	584	0.14	3595	286	0.98	5.98	59.4	1.5
	±29	±319	±0.06	±1236	±81	±0.02	±2.88	±5.5	±0.3
Vol. Exp.	82	733	0.13	5236	374	0.94	5.81	48.7	1.8
	±34	±443	±0.04	±2035	±73	±0.04	±3.23	±9.5	±0.5
Conc. Alb.	81	743	0.14	4634	397	0.92	6.44	54.5	2.7
	±32	±518	±0.05	±1805	±81	±0.04	±3.14	±8.6	±0.6

Abbreviations: CTZ = steady state collections during infusion of chlorothiazide; CTZ + EA = steady state collections during infusion of chlorothiazide and ethacrynic acid; Vol. Exp. = after infusion of iso-oncotic electrolyte solution; Conc. Alb. = during infusion of human albumin (25 g/100 ml).

[a] Values are the means of the last 3 to 6 clearance periods during each phase of the study.

excretion of sodium decreased in every patient. Changes in the excretion of potassium were variable, but on the average there was little change from the rate present during volume expansion prior to infusing hyperoncotic albumin (Table 1). In association with an increase in plasma albumin concentration averaging 0.9 g/100 ml the fraction of filtered sodium reabsorbed increased in every patient (Fig. 1, Table 1), and averaged 54.5 ± SD 8.6%.

Absolute sodium reabsorption. Although the effects of the diuretic agents, volume expansion and hyperoncotic albumin on fractional sodium reabsorption were qualitatively similar among the five patients, the absolute rate of sodium reabsorption appeared to be influenced by changes in GFR. Despite decreased fractional sodium reabsorption, the absolute rate of reabsorption after chlorothiazide alone was minimally depressed or increased in association with increased GFR (Table 1). However, after the addition of ethacrynic acid the absolute rate of sodium reabsorption was decreased below control rates in four of the five patients even though GFR (and filtered sodium) remained elevated in three of these patients (E.K., D.R. and M.L., Table 1).

The decrease in fractional sodium reabsorption following isooncotic volume expansion was associated with no change or an increase in absolute sodium reabsorption, and further increases in GFR, in three patients (E.K., D.R. and K.W., Table 1). After infusing hyperoncotic albumin the absolute rate of sodium reabsorption increased in four patients in the absence of an increase in GFR in three of the four (E.K., M.L. and G.W., Table 1). Thus, the increases in fractional sodium reabsorption after infusing hyperoncotic albumin were not dependent on directionally similar changes in GFR and filtered sodium and were associated with an increased absolute rate of sodium reabsorption in four of the five patients (Table 1, Fig. 2).

Discussion

Both clearance and micropuncture studies have demonstrated that the major effect of ethacrynic acid and chlorothiazide to block sodium reabsorption occurs in the distal nephron, predominantly the loop of Henle [3–6]. More recent micropuncture studies in the dog have demonstrated that ethacrynic acid may depress proximal tubular fractional reabsorption if urinary losses are replaced so as to prevent simultaneous volume depletion, which otherwise may counterbalance the depressant effect of the drug on proximal tubular reabsorption [14]. Even so, in the presence of these two diuretics, distal tubular reabsorption appears to be extensively blocked [3–6] while the proximal tubule appears to retain its responsiveness to maneuvers such as the infusion of saline or concentrated albumin [15]. It follows then that the fraction of glomerular filtrate reabsorbed in the proximal tubule, by determining delivery and reabsorption of sodium by the distal nephron, will influence the natriuretic effect of the diuretics [7]. In keeping with this line of reasoning, we have demonstrated previously that during the combined effect of the two agents in normal man, 30% of the filtered sodium was excreted. In striking contrast, patients with sodium retention due to cirrhosis responded to chlorothiazide and ethacrynic acid by excreting only 24% of the filtered sodium [7]. These differences in diuretic response would be expected if 1) the diuretics have minimal effects to block proximal tubular reabsorption but extensively block distal tubular reabsorption, 2) if salt loading in man depresses proximal tubular reabsorption and increases distal tubular reabsorption as has been demonstrated in experimental animals [1, 2] and 3) if the retention of sodium in patients with cirrhosis and ascites involves the reabsorption of an increased fraction of filtered sodium in the proximal tubule.

Clearance and micropuncture studies in the dog and rat indicate that proximal tubular reabsorption relates in a direct manner to the concentration of protein in the peritubular capillary circulation [8–11, 15]. If this effect obtains in man, proximal tubular reabsorption should be decreased in patients with the nephrotic syndrome and hypoalbuminemia. However, since these patients are retaining sodium and accumulating edema, reabsorption of sodium in the distal tubule would necessarily need to be increased. If so, then the natriuretic effect of distally acting diuretic agents should be exaggerated in such patients. The present results are consistent with this reasoning since in combination chlorothiazide and ethacrynic acid on the average forced the excretion of 41% of the filtered sodium.

Glomerular filtration rate in the present group of patients ranged from moderately decreased to normal. However, it does not seem likely that differences in filtration rate between these patients and the previously reported normal individuals accounted for the observed low proximal tubular fractional reabsorption in the patients with the nephrotic syndrome. There was no relationship within this group of patients between filtration rate and the value for fractional sodium

reabsorption during distal tubular blockade prior to volume expansion. Moreover, fractional sodium reabsorption in patients with cirrhosis was found to be uniformly higher than in the present patients with the nephrotic syndrome, whereas the range of filtration rates were similar in both groups [7]. The possibility cannot be excluded that the underlying renal disease in the present group of patients has some effect to decrease the fraction of filtrate reabsorbed in the proximal tubule. However, the lack of direct correlation between fractional reabsorption and severity of the renal disease (judged by filtration rate), and the effect of hyperoncotic albumin to increase fractional reabsorption argue against this possibility.

The apparent low proximal tubular fractional reabsorption in the present patients (as compared to that in normals and patients with cirrhosis) could relate to a number of factors other than the low concentrations of albumin in plasma. Filtration fraction (GFR/C_{PAH}) prior to administering the diuretic agents averaged 0.13 in the present patients compared to 0.20 in the previously studied normals and patients with cirrhosis [7]. It is unlikely then that the lowered concentration of albumin in plasma in the present patients could have been associated with a concentration of albumin in post-glomerular plasma similar to that in the previously studied patients[4]. However, the lower filtration fraction in the present patients could reflect relative efferent arteriolar vasodilation and as a result increased post-glomerular capillary hydrostatic pressure, a factor which theoretically could depress proximal tubular reabsorption [12, 16]. We hesitate to draw any conclusions regarding filtration fraction (calculated from C_{PAH}) following administration of the diuretic agents or during subsequent experimental maneuvers. E_{PAH} may be markedly influenced under such conditions and therefore C_{PAH} becomes an unreliable index of renal plasma flow [15].

Other factors which may influence overall proximal tubular fractional reabsorption such as hematocrit [17, 18] or differences in distribution of filtrate among nephrons of differing reabsorptive capacity [19, 20] could account theoretically for the apparent low rate of proximal tubular reabsorption in the present patients. Perhaps the best evidence that the low reabsorptive rates in these patients were related to the low levels of plasma albumin is the observation that fractional and absolute reabsorption increased when hyperoncotic albumin was infused. That this effect on reabsorption was due to the concentrated albumin *per se* is supported by a number of clearance and micropuncture studies demonstrating a direct relationship between proximal tubular reabsorption and the concentration of albumin in plasma [8–11, 15].

If residual tubular reabsorption of sodium in the presence of two diuretic agents represents predominantly proximal tubular reabsorption, then the present studies, in addition to showing a relationship between plasma albumin concentration and proximal tubular reabsorption, also demonstrate that iso-oncotic volume expansion can decrease proximal tubular fractional reabsorption in man. The mechanism whereby iso-oncotic volume expansion decreased fractional sodium reabsorption is not clear. GFR increased in all but one patient and a decrease in absolute reabsorption was measured in only two patients. Decreases in hematocrit could have played a role [17, 18] as could renal vasodilation [12, 16] which was evidenced by increased C_{PAH}. However, changes in GFR or C_{PAH} were not in the direction necessary to account for the increases in absolute sodium reabsorption observed after infusing hyperoncotic albumin, lending additional support to the conclusion that the concentration of albumin *per se* exerted some more direct effect on proximal tubular reabsorption in these patients. Presumably, this effect of albumin on tubular sodium reabsorption in man is mediated by changes in Starling forces operating at the level of the peritubular capillary circulation [8–11, 15, 16].

The observation that infusion of hyperoncotic albumin increased the absolute rate of tubular reabsorption in the present patients may seem at odds with other observations that infusion of albumin may produce natriuresis in patients with the nephrotic syndrome. However, in the present experimental design concentrated albumin was infused after iso-oncotic volume expansion, which had already depressed fractional sodium reabsorption and increased sodium excretion. Therefore, any effect that infusion of concentrated albumin may have to expand the vascular volume and increase sodium excretion in patients with the nephrotic syndrome may have already been achieved by the iso-oncotic infusion, permitting observation of the effect of increased plasma protein to increase sodium reabsorption and decrease sodium excretion.

The conclusion, supported by these studies, that hypoalbuminemia decreases sodium reabsorption in the proximal tubule of man necessitates the additional

[4] Although the values for plasma albumin were not reported [7], the patients with cirrhosis had concentrations greater than 3 g/100 ml and the normal individuals had values greater than 4 g/100 ml.

conclusion that sodium retention in the nephrotic syndrome must involve excessive reabsorption of sodium in the distal nephron. This interpretation is consistent with recent studies in the dog demonstrating that experimentally produced sodium retention persists despite depressed proximal reabsorption during an infusion of saline [21], indicating augmented distal tubular reabsorption in that experimental preparation. Moreover, in the present patients ethacrynic acid accounted predominantly for the exaggerated natriuretic response, suggesting that most of the sodium escaping proximal tubular reabsorption was recaptured by reabsorption in the medullary portion of the loop of Henle [3, 4]. The natriuretic effect of ethacrynic acid alone in the patients with nephrotic syndrome was to produce an excretion of sodium averaging 35% of the filtered load, whereas in a group of normals studied under similar conditions the drug produced the excretion of only 19% of the filtered sodium [7].

Because of the complex nature of the regulation of sodium reabsorption and excretion, the limited extent to which important measurements can be made in the human subject and the uncertainties involved regarding the influence of disease states or experimental maneuvers on the magnitude and sites of action of diuretic agents, the present conclusions must be considered tentative at best. These conclusions rely heavily on previous studies in animals which demonstrate more directly that volume expansion and plasma protein concentration influence proximal tubular reabsorption [1, 2, 10, 11] and that these effects may be observed by clearance techniques in the presence of the distally active diuretic agents [15]. Despite these shortcomings, the present studies are consistent with the interpretations that proximal tubular reabsorption in man relates in a direct manner to the concentration of albumin in plasma and is decreased in patients with the nephrotic syndrome and hypoalbuminemia even in the presence of sodium retention and edema formation. The latter conclusion necessitates the additional conclusion that distal tubular sodium reabsorption is markedly increased in these patients.

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