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Functional relationships in the nephrotic syndrome

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Functional relationships in the nephrotic syndrome. An analysis of 70 observations in patients with the nephrotic syndrome (NS) on a low sodium diet is presented. The following parameters were determined: plasma volume, plasma renin activity, plasma aldosterone concentration, serum albumin, urinary sodium and protein excretion, and creatinine clearance. In 41 instances glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) were determined on the basis of ^{51}Cr-EDTA and ^{125}I-hippuran clearances, and the filtration fraction (FF) was calculated. The results in patients with minimal lesions (ML) and those with histological glomerular lesions (HL) were compared to determine whether these groups can be separated on the basis of signs of hypovolemia and primary renal sodium retention. Although a higher proportion of the ML patients showed extreme sodium retention and elevated plasma renin and aldosterone levels, these values tended to overlap and no differences were found for blood volume, blood pressure, and overall renal function between the groups. FF was markedly and equally depressed in both groups: 13.5 ± 1.6% in the ML and 14.2 ± 1.1% SEM in the HL group *(NS)*. Analysis of the within-group relationships between the parameters under study revealed relatively few correlations, which supports the hypothesis that primary impairment of renal water and salt excretion is an important if not overruling factor in patients with the NS.

Relations fonctionnelles au cours du syndrome néphrotique. Une analyse de 70 observations de malades atteintes de syndrome néphrotique (NS) en régime pauvre en sodium est présentée. Les paramètres suivants ont été déterminés: volume plasmatique, activité rénine plasmatique, aldostéronémie, albuminémie, natriurèse et protéinurie, et clearance de la créatinine. Dans 41 fois, le débit de filtration glomérulaire (GFR) et le débit plasmatique rénal efficace (ERPF) ont été déterminés par des clearances au ^{51}Cr-EDTA et au ^{125}I-hippuran, et on a calculé la fraction de filtration (FF). Les résultats des groupes de malades atteints de lésions minimes (ML) et de ceux atteints de lésions glomérulaires histologiques (HL) ont été comparés pour savoir s'il est possible de séparer ces groupes sur la base des signes d'hypovolémie et de rétention sodée d'origine rénale. Bien qu'une plus forte proportion de malades ML ait présenté une réntention sodée et une élévation des niveaux de rénine et d'aldostérone plasmatiques extrêmes, ces valeurs tendaient à se chevaucher et il n'a pas été trouvé de différence dans le volume sanguin, la pression artérielle et la fonction rénale globale entre les groupes. FF était diminuée de façon marquée et identique dans les deux groupes: 13,5 ± 1,6% dans le groupe ML et 14,2 ± 1,1% SEM dans le groupe HL *(NS)*. Une analyse des interrelations à l'intérieur des groupes entre les paramètres étudiés a révélé relativement peu de corrélations, ce qui est en faveur de l'hypothèse que l'altération primitive de l'excrétion rénale d'eau et de sel est un facteur important, sinon capital chez les malades atteints de NS.

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It has been documented recently [1–3] that many patients with the nephrotic syndrome (NS) who retain sodium and water show elevated plasma volume, blood volume [4], and blood pressure, whereas the plasma renin activity and plasma aldosterone concentration are not elevated or are even depressed. This suggests that at least in these patients persistence of the edema cannot be attributed to the conventional concept of hypovolemia, but instead might be related to an intrinsic renal abnormality associated with the renal disease. This may be difficult to understand in patients whose biopsy specimens show no histological abnormalities and whose creatinine clearance is normal. Indeed, on the basis of renin-sodium profiles, Meltzer et al [2] suggested that such a primary renal impairment is especially likely in patients with histological lesions, and that the concept of undercirculation is particularly applicable to patients with minimal lesions. However, various observations in patients with minimal lesions, such as a lowered filtration fraction[1], and continued impairment of sodium excretion after blockade of the renin system [3] and hyperexpansion of the blood volume by albumin infusion [5, 6], indicate that the cause of sodium retention may also be located in the kidney in this condition.

To reach a better understanding of the pathophysiologic mechanisms that operate in the NS, we assembled pertinent data in a large number of adults with the NS who were studied under standard conditions. The questions we hoped to answer were *(1)* do correlations exist between circulatory, hormonal and renal function parameters, as would be expected on the basis of current concepts of hypovolemia, and *(2)* can basic differences be demonstrated between patients with and without histological lesions?

Methods

Patients. Seventy observations were performed in 62 patients admitted to the Utrecht University Hospital because they exhibited NS in the period from 1978 to 1983. In all but two of them the diagnosis was established by renal biopsy (light microscopy and immunofluorescence).

Minimal lesions were found in 24 patients; the diagnosis was confirmed by subsequent remission under steroid or immunosuppressive treatment. Some patients were studied more than once, that is, if a relapse occurred after complete recovery. Thus, 32 studies were done in this group of 24 patients, comprising 18 men and 6 women (mean age, 30; range, 14 to 65 years). In the other 38 patients the diagnoses were: focal glomerulosclerosis (FGSH) in eight, membranous glomeru-

lopathy (MGP) in ten, focal proliferative disease (FP) in eight, systemic lupus erythematosus (SLE) in seven, amyloidosis in three, and unknown in two. The latter were regarded as having a nonminimal-lesion nephrotic syndrome, in accordance with the clinical course of their illness. This group comprised 22 men and 16 women (mean age, 45; range, 16 to 75 years).

Studies. The criteria for inclusion in this study were patient hypoalbuminemia (<29 g/liter) and proteinuria exceeding 3.5 g/day. All patients were edemateous and without medication during at least 1 week. All were put on a low sodium (10 to 20 mmoles/day) diet immediately at admisison. Urinary sodium, creatinine and albumin excretion, blood pressure, and body weight were monitored for 3 days. On day 3, after an overnight rest, plasma volume (PV) was measured in the recumbent patient, and blood samples were taken for the estimation of plasma renin activity (PRA), plasma aldosterone concentration (PAC), creatinine, electrolytes, and albumin. PV was measured as the ^{131}I-albumin distribution volume, as described elsewhere [7]. We have shown that this technique is a valid method in the NS and overestimates PV by 1% at the most [8]. Blood volume (BV) was calculated from PV and the corrected whole-body hematocrit. Supine blood pressure was taken four times a day. The pressure at the disappearance of the Korotkoff sounds was taken as the diastolic pressure. For statistical analysis, the mean arterial pressure (MAP = diastolic pressure plus one-third pulse pressure) from eight supine measurements was used. PRA was determined by radioimmunoassay according to a modified Haber method [9]. We found that the normal range for supine normotensive healthy persons on a sodium-restricted diet is 1400 to 3000 fmoles Al/liter/sec (95% confidence limits). PAC was determined by radioimmunoassay after extraction from plasma with dichloromethane. Comparison with samples after an initial Sephadex LH-20 gel filtration step according to Nowaczynski et al [10] showed this method to be specific. Normal values for a sodium-restricted diet: 500 to 3200 pmoles/liter (95% confidence limits). Electrolytes and creatinine were determined by the standard laboratory techniques (Autoanalyzer, Technicon, Tarrytown, New York), serum albumin by cellulose-acetate electrophoresis, and protein excretion with tri-chloric acidic acid.

In 41 of the patients the effective renal plasma flow (ERPF) and glomerular filtration rate (GFR) were determined simultaneously during the constant infusion of ^{125}I-hippurate and ^{51}Cr-EDTA, in several 2-hr urine samples.

Calculations and statistics. PV, BV, and renal function parameters were normalized to lean body mass (ml/kg LBM for the volumes and clearance per 50 kg LBM for the renal functions). LBM was calculated as follows:

$$\text{LBM} = 0.407 \times \text{weight} + 26.7 \times \text{height} - 19.2 \text{ (males)} \quad (1)$$
$$\text{LBM} = 0.252 \times \text{weight} + 47.3 \times \text{height} - 48.3 \text{ (females)} \quad (2)$$

These equations are based on the regression formulas for estimating total body water in males and females [11], and the relationship LBM = 100/73 × total body water [12]. The validity has sufficiently been tested elsewhere [13]. The method requires the use of dry weight, which could be measured in most cases by making the patients edema-free shortly after the collection of our data. In a few dry weight was estimated after determination of the fluid excess with ^{82}Bromide [7].

The use of LBM (instead of body surface area or height) permits the data of both sexes to be pooled, with obvious statistical advantage. Mean PV was 56 ± 1.0 and BV 88 ± 1.4 ml/kg LBM in 51 healthy subjects investigated in our laboratory and with similar age distribution as the patients under study.

The data were stored in a Scientific Information Retrieval [14] data base and were analyzed according to the SPSS programs, with Student's *t* test and Spearman's ranking correlation test. All data are expressed as means ± SEM. In addition, the data were analyzed by multiple and partial correlation analysis using the general linear models procedures with adjustments for covariates, and with linear stepwise discriminant analysis, a multivariance technique using the Biomedical Computer Programs.

Results

Table 1 presents the means of all 70 observations, arranged in groups according to sodium excretion, creatinine clearance, and the presence or absence of histological lesions. Judged from sodium excretion, most subjects were in or near sodium balance shortly after admission (group A, 28 ML and 24 HL). In a smaller group (group B, 4 ML and 14 HL, of whom one had FGSH, four SLE, one amyloidosis, four FP, three MGP and one unknown) the daily sodium excretion exceeded the intake by more than 20 mEq but was still low relative to the edema in the group. Mean protein loss and PAC were higher in group A, whereas PV, BV, and MAP were comparable and in or above the normal range. Mean PRA and PAC were in the range of a normal-to-moderate sodium intake.

Because we were particularly interested in the factors that determine the sodium retention in the NS, we limited additional analysis to the 52 subjects in group A. Comparsion of patients with ML (group C) and with HL (group D) revealed a lower serum albumin with a tendency to stronger proteinuria, and a higher PAC with a tendency to a higher PRA in the ML-group. In this group the PV, but not the BV, was lower.

Subdivision of groups C and D according to renal function (judged as normal or moderately decreased when creatinine clearance was > 80 ml/min) showed impaired renal function in 10 ML (group F) and in 15 HL (group H) patients. Histological diagnosis in the latter were FGSH in four out of six patients, SLE in three out of four, amyloidosis in one out of three, FP in one out of two, MGP in five out of eight, and unknown in one out of one.

The finding of relatively lower serum albumin in MLNS proved to be independent of renal function, but the higher PAC was only evident in case of normal renal function (group E vs. G). Within the group with ML, renal impairment was associated with tendencies for higher PV, BV, and MAP and lower values for PAC and PRA (group F vs. E). In the patients with HL this tendency was observed for the MAP only (group H vs. G).

In seven ML subjects, all belonging to group E, the PRA was elevated as in normals on a 20 mEq sodium diet (PRA > 1400 fmoles/l · sec). These subjects, distinguished as group E_a in Table 1, also had a stimulated PAC, but BV, MAP, and plasma albumin were not different from the others of this subset (group E_b). In four patients with HL, two of whom had amyloidosis, the PRA was similarly stimulated. Because of large differences in sodium excretion and renal function, we did not arrange them in a separate group.

Table 1. Data of 70 episodes of the nephrotic syndrome in 62 patients

Subset[b]	N	Males	Age *years*	PV *ml/kg*	BV *ml/kg*	MAP *mm Hg*	PRA *fmoles/liter/sec*	PAC *pmoles/liter*	C_{Cr} *ml/min*	Alb *g/liter*	Na excr *mmoles/day*	Prot excr *g/day*
A ML and HL	52	37	36.9	65	96	101	560	330	72	18	17	10.4
low Na-excr			(14–75)	2	2	2	150	90	5	1	2	1.0
B ML and HL	18	16	40.2	63	91	106	440	140	73	21	103	8.1
high Na-excr			(19–69)	3	3	4	140	20	7	2	10	1.8
C ML	28	22	28.9	62	97	101	700	460	80	15	12	10.9
low Na-excr			(14–65)	2	3	2	250	210	6	1	3	1.2
D HL	24	15	46.8	67	96	101	440	220	63	21	24	8.8
low Na-excr			(18–75)	2	3	3	130	40	7	1	3	0.8
E ML low Na-excr	18	15	24.7	59	94	98	780	680	100	16	12	11.5
normal Ccreat			(14–65)	3	4	3	410	400	4	1	3	1.1
E_a ML low Na-excr	7	5	21.9	56	92	95	2820	1320	100	14	3	15.1
normal Ccreat high PRA			(14–33)	3	6	6	1110	650	7	1	1	2.0
E_b ML low Na-excr	11	10	27.5	60	95	99	350	190	99	16	17	9.1
normal Ccreat low PRA			(17–65)	3	5	2	80	80	5	1	5	1.0
F ML low Na-excr	10	7	31	67	103	106	550	240	44	14	13	12.0
low Ccreat			(16–58)	2	3	4	240	200	6	1	5	1.0
G HL low Na-excr	9	7	48.3	67	95	96	480	240	97	20	27	7.3
normal Ccreat			(25–75)	3	6	3	230	30	7	2	5	0.5
H HL low Na-excr	15	8	45.9	67	94	104	430	210	43	20	23	9.8
low Ccreat			(18–71)	3	3	4	170	70	5	1	4	1.2
P value A vs. B				*NS*	*NS*	*NS*	*NS*	0.001	*NS*	0.01	0.001	0.025
C vs. D				0.04	*NS*	*NS*	*NS*	0.001	0.06	0.001	*NS*	*NS*
E vs. F				0.004	0.06	0.05	*NS*	0.04	0.001	*NS*	*NS*	*NS*
E vs. G				0.01	*NS*	*NS*	*NS*	0.02	*NS*	0.03	0.001	0.002
F vs. H				*NS*	0.04	*NS*	*NS*	*NS*	*NS*	0.001	*NS*	*NS*
G vs. H				*NS*	*NS*	*NS*	*NS*	*NS*	0.001	*NS*	*NS*	*NS*
E_a vs. E_b				*NS*	*NS*	*NS*	0.001	0.001	*NS*	*NS*	0.01	0.005

Abbreviations: PV, plasma volume; BV, blood volume; MAP, mean arterial pressure; PRA, plasma renin activity; PAC, plasma aldosterone concentration; C_{Cr}, clearance of creatinine; Alb, albumin; Na excr, sodium excretion; Prot excr, protein excretion; ML, minimal lesions; HL, histological lesions; *NS*, not significant.

[a] Data are expressed as mean ± SEM, except age which is given as the mean and range.

[b] Subsets A and B comprise all patients with ML or HL with a low and high sodium excretion, respectively. C and D are respectively ML and HL patients with a low sodium excretion; E and F ML patients with a low sodium excretion and a normal (E) or low (F) C_{Cr}; G and *H* those HL patients with a low sodium excretion and a normal (G) or low (H) C_{Cr}, and E_a and E_b are the same patients as in E, now divided into high and low PRA groups, respectively.

Discriminate analysis. Discriminant analysis, including all the variables given in Table 1, showed that patients with ML and HL could be distinguished with 80% accuracy with the equation:

$$d = -0.110 \times \text{Albumin} + 0.127 \times \text{Albumin excretion} - 0.033 \times \text{Age} + 1.993,$$

or, after exclusion of age, with the equation:

$$d = 0.016 \times \text{creatinine clearance} - 0.111 \times \text{Albumin} - 0.010 \times \text{sodium excretion} + 0.128 \times \text{Albumin excretion} - 0.006$$

($d > 0$ for ML, $d < 0$ for HL, units as in Tables 1).

Correlations. Because multiple regression analysis did not substantially alter the calculated correlations and did not add to the understanding of the pathophysiological mechanisms, all correlations are presented as Spearman's ranking correlation coefficients. Correlations were calculated for each of the ML and HL groups separately and for all patients together. The main results, including all significant correlations, are given in Table 2. In general, there was a striking absence of correlation. For example no correlation was found between the plasma albumin level and either BV (Fig. 1) or PRA, or between BV and PRA (Fig. 2). There was a significant negative correlation between PAC and sodium excretion ($r = 0.52$, $P < 0.001$) for the whole group. A significant negative correlation was also found between PAC and BV ($P < 0.05$), but only in the ML group. MAP was positively correlated with BV ($P < 0.05$) in this group. There was a more striking relationship between MAP and PAC that was also present in the HL group. As could be expected, there was a highly significant correlation between PRA and PAC in both groups.

Renal function tests. In 19 patients with ML and 22 with HL, representative for the larger groups shown in Table 1, the GFR and ERPF were measured simultaneously. In the patients with ML mean GFR was 74 ± 9 and ERPF 595 ± 44 ml/min. In the subjects with HL the mean values were 65 ± 7 and 469 ± 37 ml/min, respectively. Figure 3 shows that the ranges largely overlap, and that on the average the filtration fraction (FF) is equally reduced in the two groups: 13.5 ± 1.6 in patients with ML and 14.2 ± 1.1% in patients with HL. The correlations between renal hemodynamics on the one hand, and BV, PRA, PAC, MAP, plasma albumin, and sodium excretion on the other are summarized in Table 3. The significant correlation between ERPF and GFR in the HL subjects is strikingly absent

Table 2. Relationships[a] in the nephrotic syndrome

	ML ($N = 32$)	HL ($N = 38$)	All patients ($N = 70$)
Serum albumin vs.			
Blood volume	−0.12	0.19	−0.05
Log PRA	−0.04	−0.09	−0.16
Log PAC	−0.12	−0.10	−0.30[b]
MAP	−0.21	0.18	0.06
Na-excretion	0.30	0.15	0.47[c]
Blood volume vs.			
Log PRA	−0.16	−0.09	−0.11
Log PAC	−0.52[b]	0.20	−0.09
MAP	0.45[b]	0.09	0.25
Na-excretion	−0.12	0.06	−0.07
Log PRA vs.			
Log PAC	0.80[d]	0.43[b]	0.65[d]
MAP	−0.06	−0.34	−0.20
Na-excretion	−0.27	−0.01	−0.22
Log PAC vs.			
MAP	−0.50[c]	−0.47[c]	−0.45[c]
Na-excretion	−0.35	−0.43[b]	−0.52[d]
MAP vs.			
Na-excretion	0.03	0.003	0.03

Abbreviations: See Table 1.
[a] Relationships are expressed as Spearman's correlation coefficient.
[b] $P < 0.05$.
[c] $P < 0.01$.
[d] $P < 0.001$.

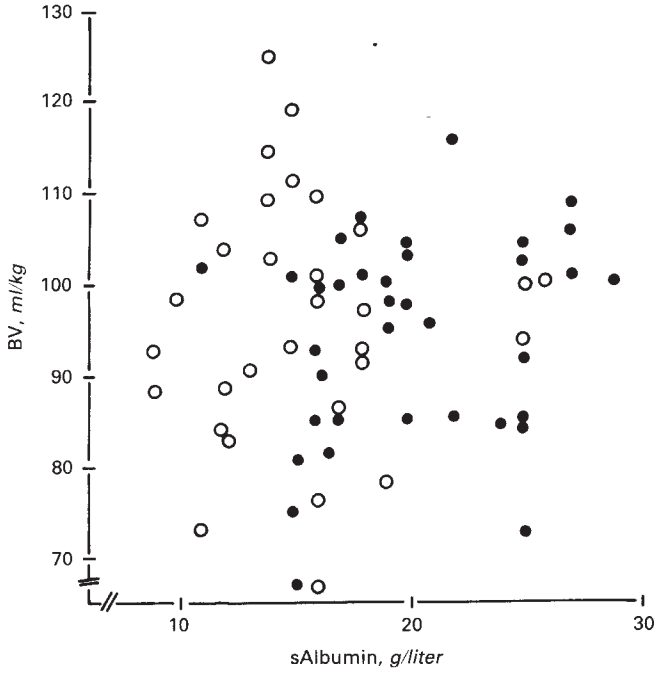

Fig. 1. *Scattergram of blood volume (BV, normalized to lean body mass, ml/kg) and serum (s) albumin (g/liter) in nephrotic syndrome patients.* No correlation was found. Symbols are: ○, minimal lesions; ●, histological lesions.

in the ML group. In both groups FF correlated well with GFR, whereas correlation with ERPF was absent. PRA was correlated with GFR and FF, the PAC only with GFR. A negative correlation between BV and GFR was only found in the patients with ML, and between plasma albumin and ERPF in all of the groups.

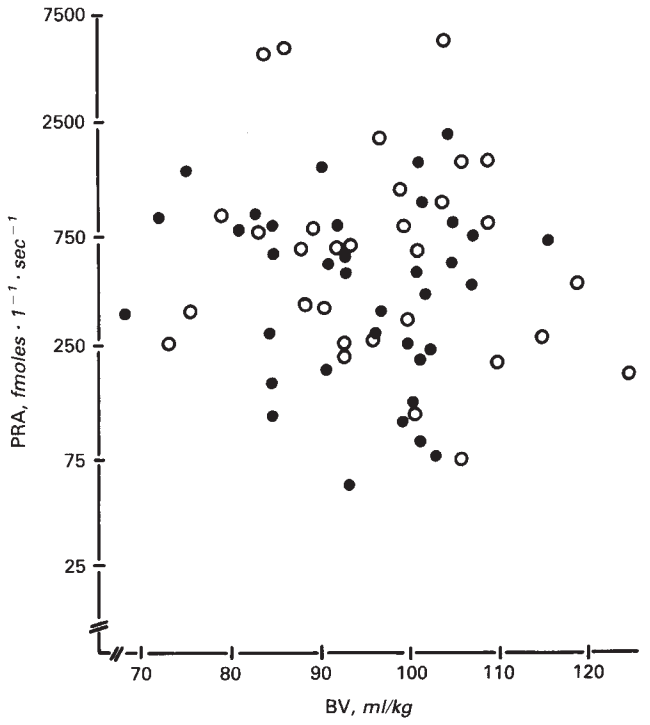

Fig. 2. *Scattergram of plasma renin activity (PRA, fmoles/liter/sec) and blood volume (BV, normalized to lean body mass ml/kg) in patients with the nephrotic syndrome.* No correlation was found between these two variables. Symbols are: ○, minimal lesions; ●, histological lesions.

Discussion

The main purpose of this study was to investigate differences and similarities between the factors considered to be involved in fluid retention in the NS in the absence of histological lesions (minimal lesions, ML) as compared with the NS characterized by histological lesions (HL), with special attention to the role of functional hypovolemia.

All NS patients admitted to our department during the past 5 years were studied under conditions of a 20-mEq sodium diet. Most of the patients reached sodium balance rapidly on this diet (group A, Table 1). The others (group B) showed some sodium excretion, generally moderate relative to their edema, and lower levels of mean PAC. This finding, also made by other investigators [15, 16], contrasted with the similarity in creatinine clearance as well as the other indicators of the volume status, such as PV, BV, MAP, and PRA. It is therefore unlikely that the stronger sodium retention in group A is attributable to a relative hypovolemia.

Group A comprised almost equal numbers of subjects with ML (group C) and with HL (group D). Comparison revealed that the patients with ML generally tended to stronger sodium retention, lower serum albumin, and higher mean aldosterone values, but had similar blood volume and PRA. Mean blood pressure was relatively high in both groups. Although these

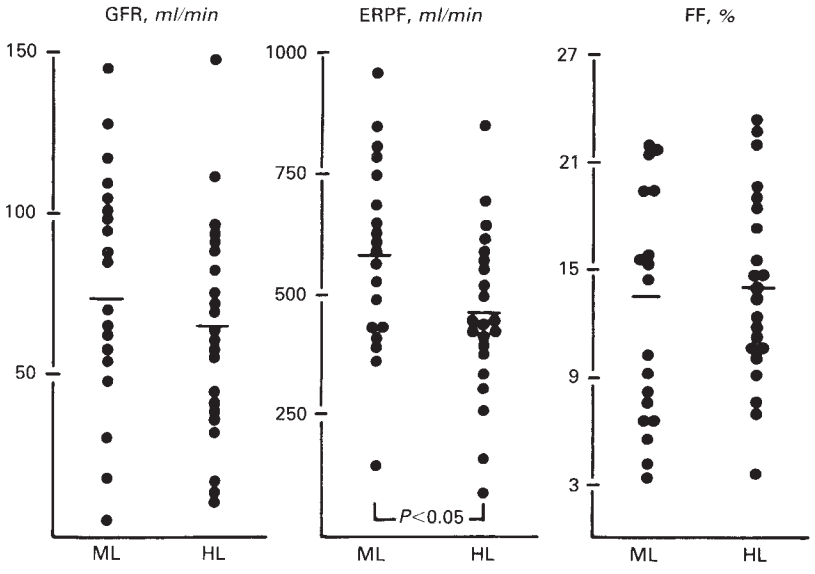

Fig. 3. *GFR, ERPF, and FF values in patients with ML (N = 19) and HL (N = 22).* GFR and ERPF are normalized to a 50-kg lean body mass.

Table 3. Relationships[a] between renal functions and other pertinent data in the nephrotic syndrome

	ML (N = 19)	HL (N = 22)	Total (N = 41)
GFR vs.			
ERPF	0.09	0.65[d]	0.44[c]
FF	0.86[d]	0.64[d]	0.73[d]
BV	−0.42[b]	0.01	−0.19
Log PRA	0.63[c]	0.22	0.44[c]
Log PAC	0.53[b]	0.33	0.50[c]
MAP	−0.30	−0.50[c]	−0.45[c]
Serum albumin	0.05	−0.18	−0.16
ERPF vs.			
FF	−0.27	−0.04	−0.15
BV	−0.02	−0.16	−0.08
Log PRA	−0.13	−0.14	0.01
Log PAC	0.09	0.22	0.29
MAP	−0.16	−0.44[b]	−0.33[b]
Serum albumin	−0.42[b]	−0.44[b]	−0.55[d]
FF vs.			
BV	−0.33	0.26	−0.13
Log PRA	0.51[b]	0.45[b]	0.47[c]
Log PAC	0.45[b]	0.17	0.27
MAP	−0.39[b]	−0.43[b]	−0.35[b]
Serum albumin	0.17	0.07	0.18

Abbreviations: ERPF, effective renal plasma flow; FF, filtration fraction; for other abbreviations, see Table 1.

[a] Correlations are expressed as Spearman's rank correlation coefficient.

[b] $P < 0.05$.

[c] $P < 0.01$.

[d] $P < 0.001$.

mean values do not indicate functional hypovolemia, we considered the possibilty that hypovolemia plays a role in individual cases, especially within the ML group. After further subdivision according to creatinine clearance, the pattern changed slightly in that the difference in PAC only persisted in those subjects with normal renal function, and the highest values for PRA and PAC were found in the group with ML and normal creatinine clearance (group E). Because this group might contain patients who satisfy the criteria for functional hypovolemia most closely, we selected from it seven patients with markedly elevated renin and aldosterone levels (group E_a). Indeed, their mean blood volume and blood pressure values tended to be lower than those of the others, but were not below normal, and these patients did not appear to be hypovolemic on clinical grounds. The other subjects in this group (group E_b) had normal PRA and PAC, and thus could not be considered hypovolemic by any standard.

The finding of a stimulated renin-angiotensin system was not limited to the ML group, but was also made in four subjects with HL, two of them suffering from amyloidosis. Therefore, it is evident from the analysis thus far that there is no basic difference between patients with and without glomerular lesions with respect to the factors responsible for sodium retention, albeit that the frequency of elevated PRA and PAC was higher and that of reduced renal function lower among patients with ML. In most of the subjects, PRA and PAC were relatively low, and neither blood volumes nor blood pressures decreased. This pattern was found in ML and HL, irrespective of renal function except that in both groups a lower glomerular filtration was accompanied by higher blood pressure.

Our findings agree with those of Meltzer et al [2], in that high renin levels may occur in some patients with MLNS. However, we also found that an elevated PRA does not necessarily indicate functional hypovolemia, and it is certainly not permissible to classify ML patients as having a high-renin-underfilling type of NS. Most behaved like patients with HL, and fulfilled criteria for hypervolemia rather than for hypovolemia.

To allow comparison of the largest possible numbers, we did not differentiate the groups according to age or sex. The latter was permissible because the relevant variables were normalized to lean body mass calculated individually for males and females. The mean age, but not the range, was lower in those with ML. However, since aging is generally accompanied by a fall in PRA and a rise in blood pressure, a correction for age could only have strengthened our conclusion that most sub-

jects with ML behaved like hypervolemic rather than hypovolemic patients.

Discriminant analysis revealed that the ML patients tended to have a lower age and more severe proteinuria, but gave no clue for different mechanisms of sodium retention between patients with ML and HL. After exclusion of age, this analysis showed that the MLNS is characterized by the combination of a generally higher creatinine clearance and more severe proteinuria and sodium retention, but it did not reveal differences in the volume parameters studied.

The correlation analysis yielded little support for the assumption that fluid retention in the NS follows the classical pathway, that is, proteinuria leading to renal sodium retention via a decrease of the serum albumin, plasma volume, and blood volume, and stimulation of the renin-angiotensin-aldosterone system. For example, no significant correlations were found between the decrease in serum albumin and either plasma or blood volume (Fig. 1), which confirms reports by other investigators [3, 17, 18]. There was also no correlation between blood volume and PRA (Fig. 2). The only correlations found were between sodium excretion and serum albumin (positive) and PAC (negative), when all observations were taken together (Table 2). This lack of correlation cannot, however, be taken as conclusive evidence against functional hypovolemia for several reasons. First, it must be kept in mind that "it is in the nature of homeostatic mechanisms that the regulated values are kept nearly constant" [19]. Second, as recently pointed out [20], patients with the NS probably represent a spectrum of pathophysiologic abnormalities, ranging from an overfilled circulation with nephritic elements to functional hypovolemia secondary to renal protein loss. These elements may not be mutually exclusive, and both participate to different degrees in the volume retention of individual patients, whether or not there are visible glomerular lesions. According to the prevailing mechanism, opposite alterations in blood volume, blood pressure, and renin may occur. This makes it unlikely that unequivocal correlations will be found in even as large a series of NS patients as the one presented here.

The finding of a similar low filtration fraction in patients with ML and patients with HL (Fig. 3) offers the strongest evidence of a primary renal disturbance of volume regulation in this condition, since functional hypovolemia is associated with a high filtration fraction [20]. Moreover, a reduced plasma oncotic pressure tends to enhance glomerular filtration [21], and the true glomerular damage may remain partly concealed. The relative increase in renal blood flow, also demonstrated in experimental glomerulonephritis [22], compensates for the filtration impairment. As a result, GFR may be normal or slightly reduced, but, obviously, this does not mean that the sodium retention could not be primarily due to kidney dysfunction.

Finally, the behavior of the PRA deserves special attention. It is not clear why the PRA is greatly elevated in some patients and not in others. Medina et al [23] suggested that the lack of substrate causes a relatively low PRA in some cases, but this seems unlikely [24]. The positive correlations that we found between the PRA or PAC and the ^{51}Cr-EDTA clearance suggest that a renin factor participates in the sodium retention particularly in case of a relatively normal renal function. Elevated renin levels, however, appeared to be unaltered by changes in sodium intake in subjects with ML [2] or HL [25]. On the other hand, in patients with low renin changes in sodium intake were shown to induce normal changes in PRA, thus indicating a normal reaction of the juxtaglomerular apparatus to volume changes [2]. These results, as well as the recent report by Brown et al [3] that active sodium retention may occur in the NS in the absence of a stimulated renin-angiotensin-aldosterone system, raise doubts as to the role of this system in sodium retention, and suggest that, at least in some patients, renin release is mediated by an unknown mechanism. Factors such as low plasma oncotic pressure [26, 27] and a low solute delivery to the macula densa due to an increased proximal tubular reabsorption [5, 28] may play a role. Increased prostaglandin production, mediating local vasodilatation and increased renal blood flow [22], may also be involved.

In sum, analysis of a large group of patients with the NS showed that in all probability the mechanism underlying sodium retention in patients with ML is essentially the same as that in patients with HL. In both, a primary renal disturbance, most probably related to a decrease of the filtration fraction, was operative, whereas a relatively small number of ML patients showed indications of edema due to hypovolemia. Because both mechanisms may be operative to a variable degree in each subject, consistent correlations between hemodynamic parameters, the renin-aldosterone system, and sodium excretion, are not likely to be encountered. The situation is even more complicated for the PRA because here nonvolume-related intrarenal mechanisms probably exert an influence as well.

The interpretation of these findings is limited by the fact that they were made randomly in an established steady state condition. Further insight can probably be acquired by a more dynamic approach, that is, analysis of the sequence of alterations occurring after spontaneous or induced changes in this steady state.

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References

1. Dorhout Mees EJ, Roos JC, Boer P, Oei YH, Simatupang TA: Observations on edema formation in the nephrotic syndrome in adults with minimal lesions. *Am J Med* 67:378–384, 1979
2. Meltzer JI, Keim HJ, Laragh JH, Sealy JE, Kung-Ming J, Chien S: Nephrotic syndrome: vasoconstriction and hypervolemic types indicated by renin-sodium profiling. *Ann Intern Med* 91:688–696, 1979
3. Brown EA, Markandu ND, Roulston JE, Jones BE, Squires M, McGregor GA: Is the renin-angiotensin system involved in the sodium retention in the nephrotic syndrome? *Nephron* 32:102–107, 1982
4. Eisenberg S: Blood volume in persons with the nephrotic syndrome. *Am J Med Sci* 255:320–326, 1968
5. Koomans HA, Geers AB, Meiracker vd AH, Roos JC, Boer P, Dorhout Mees EJ: Effect of plasma volume expansion on re-

nal salt handling in patients with the nephrotic syndrome. *Am J Nephrol* 4:227–234, 1984
6. Brown EA, Sagnella GA, Jones BE, Markandu ND, Squires M, McGregor GA: Evidence that some mechanisms other than the renin system causes sodium retention in the nephrotic syndrome. *Lancet* 2:1237–1240, 1982
7. De Planque BA, Geyskes GG, Dongen van R, Dorhout Mees EJ: Simultaneous determination of extracellular volume and blood volume with the Volumetron. *Clin Chim Acta* 11:270–277, 1965
8. Geers AB, Koomans HA, Boer P, Dorhout Mees EJ: Plasma and blood volumes in the nephrotic syndrome. *Nephron* 38:170–174, 1984
9. Haber E, Koerner T, Page LB, Kliman B, Purnode A: Application of a radioimmunoassay for angiotensin I to the physiologic measurement of plasma renin activity in normal human subjects. *J Clin Endocrinol Metab* 29:1349–1355, 1969
10. Nowaczinsky W, Sasaki C, Genest J: Radioimmunoassay for aldosterone and normal values under various physiological conditions. *J Steroid Biochem* 5:123–131, 1974
11. Hume R, Weyers E: Relationship between total body water and surface area in normal and obese subjects. *J Clin Pathol* 24:234–238, 1971
12. Rathbun EN, Pace N: Studies on body composition. I. The determination of total body fat by means of the body specific gravity. *J Biol Chem* 158:667–676, 1945
13. Womersley J, Boddy K, King PC, Durnin JGVA: A comparison of the fat-free mass of young adults estimated by anthropometry, body density and total potassium content. *Clin Sci* 43:469–475, 1973
14. Robinson BA, Anderson GD, Cohen E, Gazdzink WF: *Scientific Information Retrieval* (2nd ed). Evanston, Illinois, Sir Inc, 1979
15. Oliver WJ: Physiologic response associated with steroid-induced diuresis in the nephrotic syndrome. *J Lab Clin Med* 62:449–464, 1963
16. Reubi FC, Weidmann P, Glück Z: Interrelationships between sodium clearance, plasma aldosterone, plasma renin activity, renal hemodynamics and blood pressure in renal disease. *Klin Woschenschr* 57:1273–1285, 1979
17. Jensen H, Rossing N, Andersen SB, Jarnum S: Albumin metabolism in the nephrotic syndrome in adults. *Clin Sci* 33:445–457, 1967
18. Krishna GG, Danovitch GM: Effects of water immersion and renal function in the nephrotic syndrome. *Kidney Int* 21:395–401, 1982
19. Epstein EH: Underfilling versus overflow in hepatic ascites *(editorial). N Engl J Med* 307:1577, 1982
20. Glassock RJ, Cohen AH, Bennet CM, Martinez-Maldonado M: Primary glomerular diseases, in *The Kidney* (2nd ed), edited by Brenner BM, Rector FC, Philadelphia, London, Toronto, W.B. Saunders and Company, 1981
21. Scheurlen PG, Klaus D: Flussigkeitshaushalt und volumenregulation extremen serum albumin mangel (Analbuminämie). *Klin Wochenschr* 38:123–126, 1960
22. Bennet CM, Thompson GR, Glassock RJ: Sodium-homeostasis in acute glomerulonephritis. *Miner Electrolyte Metabol* 2:63–69, 1979
23. Medina A, Davies DL, Brown JJ, Fraser R, Lever AF, Mallick NP, Morton JJ, Robertson JIS, Free M: A study of the renin angiotensin system in the nephrotic syndrome. *Nephron* 12:233–239, 1974
24. Boer P, Roos JC, Geyskes GG, Dorhout Mees EJ: Observations on plasma renin substrate in the nephrotic syndrome. *Nephron* 26:121–125, 1980
25. Chonko AM, Bay WH, Stein JH, Ferris TF: The role of renin and aldosterone in salt retention of edema. *Am J Med* 63:881–889, 1977
26. Hall JE, Guyton AC: Changes in renal hemodynamics and renin release caused by increased plasma oncotic pressure. *Am J Physiol* 231:1550–1556, 1976
27. Cohen AJ, Spokes K, Brown RS, Stoff JS, Silva P: Stimulation of renin release by hyperoncotic perfusion of the isolated rat kidney. *Circ Res* 50:400–404, 1982
28. Vander AJ, Miller R: Control of renin secretion in the anesthetized dog. *Am J Physiol* 207:537–546, 1964