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Preservation of blood volume during edema removal in nephrotic subjects

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Preservation of blood volume during edema removal in nephrotic subjects. During the gradual removal of edema with diuretics in 21 edematous patients with the nephrotic syndrome (NS) we monitored blood volume. For comparison, nine healthy subjects were studied after equilibration on diets containing 20, 200, and 1138 mEq sodium. The initial extracellular fluid volume (ECFV) in the patients exceeded the final ECFV by 63.4 ± 8.4%. In 10 patients with a very low plasma oncotic pressure (8.2 ± 0.4 mm Hg, Group 1), the blood volume changed little. In Group 2 (plasma oncotic pressure 13.4 ± 1.0 mm Hg), it was 11.0 ± 2.5% higher at entry than after edema withdrawal. In the normal volunteers, the highest sodium intake raised the ECFV by 21.4 ± 4.1%. The accompanying rise in blood volume, 11.2 ± 3.0%, was larger than in the patients of Group 1 (2.4 ± 1.9%, $P < 0.04$), but not of Group 2 (8.1 ± 1.9%, NS) at similar degrees of expansion. There was no difference in blood volume between the edema-free patients and the normal subjects at low-sodium diet. The course of blood pressure and creatinine clearance during edema removal gave no evidence that functional hypovolemia was induced, but the plasma renin activity was higher than in the normal subjects at similar degrees of expansion. We conclude that the blood volume to ECFV relationship curve is flattened in the presence of hypoalbuminemia. Thus, the increase in blood volume that normally follows ECFV expansion is less in patients with the NS, but a drop below normal upon removal of edema is absent also.

Préservation du volume sanguin au cours de la suppression des oedèmes chez les sujets néphrotiques. Au cours de la suppression progressive des oedèmes par des diurétiques chez 21 malades oedémateux atteints de syndrôme néphrotique (NS) nous avons surveillé le volume sanguin. A titre de comparaison, neuf sujets sains ont été étudiés après équilibration avec des régimes contenant 20, 200, et 1138 mEq de sodium. Le volume liquidien extracellulaire (ECFV) initial des malades dépassait l'ECFV final de 63,4 ± 8,4%. Chez 10 malades ayant une pression oncotique plasmatique très basse (8,2 ± 0,4 mm Hg, Groupe 1) le volume sanguin a peu changé. Dans le Groupe 2 (pression oncotique plasmatique 13,4 ± 1,0 mm Hg) il était de 11,0 ± 2,5% plus élevé au début qu'après la suppression des oedèmes. Chez les volontaires sains, l'apport sodique le plus élevé a augmenté ECFV de 21,4 ± 4,1%. L'élévation associée du volume sanguin, 11,2 ± 3,0%, était plus grande que chez les malades du groupe 1 (2,4 ± 1,9%, $P < 0,04$) mais non chez ceux du groupe 2 (8,1 ± 1,9%, NS) pour des degrés semblables d'expansion. Il n'existait pas de différence de volume sanguin entre les malades sans oedème et les sujets normaux au régime pauvre en sodium. L'évolution de la pression sanguine et de la clearance de la créatinine au cours de la suppression des oedèmes n'a pas fourni de preuve qu'une hypovolémie fonctionnelle était induite, mais l'activité rénine plasmatique était plus élevée que chez les sujets normaux pour des degrés semblables d'expansion. Nous concluons que la courbe reliant le volume sanguin à ECFV est aplatie en présence d'une hypoalbuminémie. Ainsi, l'augmentation du volume sanguin qui suit normalement une expansion de ECFV est moindre chez les malades atteints de NS, mais la chute en-dessous de la normale lors de la suppression des oedèmes est également absente.

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A number of studies have emphasized that in patients with edema due to the nephrotic syndrome (NS) the blood volumes are often within normal limits [1–4]. At first sight, this observation seems in contradiction to the conventional view that the fluid retention in the NS is secondary to a reduction in circulating volume connected with the hypoproteinemia. However, as was recently stated by Epstein [5], one should consider that "it is in the nature of homeostatic mechanisms that the regulated values are kept nearly constant." Therefore, it is conceivable that the intravascular normovolemia in patients with the NS is purely a result of secondary fluid retention.

Evidently, this consideration implies that creation of edema-free conditions in patients with the NS forms a threat to their circulating volume and hence produces a potentially dangerous situation. Indeed, in the one study dedicated to this issue [6], it was demonstrated that treatment of nephrotic subjects with diuretics often caused a reduction of the blood volume below the predicted normal value, and, in some occasions, caused postural hypotension. By contrast, in some of the patients there was an augmentation in blood volume. The improvement of renal function during edema removal observed by Lowenstein, Schacht, and Baldwin [7] is also not consistent with the generation of functional hypovolemia. In addition, recent reports on reductions in colloid osmotic pressure in tissue fluid parallel to that in plasma in several forms of protein depletion [8–11] suggest that there is no reason for a reduced blood volume, even in edema-free conditions.

We presently report a series of patients with the NS who were studied during treatment with diuretics until they were free of edema. Attention was paid to degree of hypoproteinemia, blood volume, blood pressure, renal function, and renin activity, and the results were compared with studies in nine normal volunteers in whom expansion was produced by an extremely high NaCl intake (> 1000 mmole/day). It was found that, relative to the degree of volume retention, the blood volume expands less in NS patients than in normals, particularly so in the case of severe hypoproteinemia. On the other hand, it does not drop below normal in edema-free conditions, and signs of functional hypovolemia fail to appear.

Methods

Patients

Twenty-one patients with the NS (16 men, five women) were studied, ranging in age from 17 to 72 yrs (mean 39 yrs). The cause of the NS was minimal lesions in seven, focal segmental sclerosis in three, membraneous glomerulopathy in six, mesangiocapillary glomerulopathy in three, amyloidosis in one, and systemic lupus erythematosus in one. The nine normal volunteers (six men, three women), had a mean age of 23 yrs (range from 21 to 26 yrs). Informed consent was obtained from all individuals.

Study protocol

Nephrotic patients. All patients were admitted to the hospital and placed on a diet containing 20 mmole of sodium daily. The majority was free of medication; in the others, medication was discontinued at admission. On the third day, plasma and extracellular fluid volume (ECFV) were measured after the patients had been supine and fasting overnight. Blood was drawn for determination of plasma renin activity (PRA), colloid osmotic pressure, total protein, and albumin. Blood pressure was taken semiautomatically (Arteriosonde 1217, Hoffman la Roche Inc., Cranbury, New Jersey, USA) and the mean of six determinations during 3 hrs was recorded. The following days, the patients received diuretics (mostly a combination of furosemide, chlorthalidone, and amiloride) until the edema had decreased markedly. At that moment, the diuretics were withheld for 2 days and the initial measurements repeated. This procedure was repeated when the patients were "dry", estimated by clinical signs and confirmed by ECFV measurements. Thus, in each subject, at least three sets of measurements were obtained, but, in some, the studies were done more often during the period of volume removal. During the whole period of study, lasting from 14 to 30 days, body wt, blood pressure, and 24-hr creatinine, sodium, and protein excretion were recorded.

Normal controls. The normal volunteers were studied after equilibration on a 20 mEq and a 200 mEq sodium diet during 2 successive weeks on outpatient basis. The third sodium intake level was adjusted to their glomerular filtration rate, estimated from 24-hr creatinine clearance, and amounted to 1138 (916 to 1224) mEq sodium daily. Of this sodium intake, 300 mEq were taken orally, and the residual amount was infused as isotonic saline equally over the day from 7 A.M. until midnight. On the last day of each period, the same measurements were performed as in the nephrotic patients, except for the fluid volumes, which were determined only during both extreme sodium intakes. Twenty-four-hr urine collections were made for determination of sodium and creatinine. Both patients and the normal controls were ambulant except for the morning of study.

Laboratory. The blood samples were collected in pre-chilled tubes containing EDTA and centrifuged at 4°C immediately. PRA was measured by radioimmunoassay according to a modification of the method described by Haber et al [12].

ECFV was measured as the 82-Br space, with corrections for penetration of bromide in the erythrocyte and for Donnan's equilibrium [13]. Plasma volume was measured with ^{131}I-tagged albumin, taking a single 20 ml blood sample 10 min after injection [13]. Blood volume was calculated from plasma volume and whole body hematocrit. The validity of this method to estimate plasma and blood volume in patients with the nephrotic syndrome has been demonstrated by us in a recent study [2]. The fluid volumes were expressed as liters normalized to a lean body mass (LBM) of 50 kg. LBM was estimated from height and edema-free weight [14]. Values for blood volume and ECFV as estimated in our laboratory in normal volunteers on a liberal salt intake are 4.4 ± 0.4 and 15.1 ± 0.9 l/50 kg LBM (mean ± SD), respectively (N = 56, age 19 to 72 yrs).

The colloid osmotic pressure was determined with an Oncometer (CCMI, Los Angeles, California, USA). Protein, creatinine, and electrolytes were determined by standard laboratory techniques. Albumin was determined from total protein and gel electrophoresis.

Calculations. Intra-individual changes were evaluated with a paired Wilcoxon test, and intergroup differences with a nonpaired Wilcoxon test. Correlations were detected by linear regression analysis and differences between lines by covariance analysis. All values are given as means + SEM.

Results

Patients with the nephrotic syndrome

To evaluate the effects of a lowered plasma colloid osmotic pressure, we subdivided the patients in two groups: Group 1 contained ten patients with a plasma colloid osmotic pressure below 11 mm Hg during the whole study, and Group 2, 11 patients with values exceeding 11 mm Hg at admission or during volume removal.

Within Group 1 were six patients with minimal lesions, mean age 20 yrs (range 16 to 27 yrs), two patients with membraneous glomerulopathy (67 and 72 yrs), one patient with amyloidosis (71 yrs), and one patient with focal sclerosis (23 yrs). Group 2 included one patient with minimal lesions (18 yrs); the remaining subjects within this group had histological lesions, their mean age being 46.5 yrs (range 29 to 67 yrs).

In all cases, it appeared possible to attain the edema-free state, the mean weight loss being 10.9 kg (5 to 20 kg) in Group 1 and 8.2 kg (4 to 22 kg) in Group 2. The blood pressure generally decreased, the total fall being significant in both groups. Orthostatic hypotension was observed in two patients of Group 1: in one 71-yr-old male subject, suffering from amyloidosis, and one 16-yr-old boy, suffering from steroid-resistant minimal change NS. The latter patient suffered from adrenal insufficiency due to long-standing steroid administration. After discontinuing steroids, a tendency for postural hypotension had developed. In both, postural hypotension was also present before fluid removal. Creatinine clearance was below normal in most patients, and showed a modest but significant further fall during diuretic treatment in both groups.

Table 1 presents the data obtained in the two groups during maximal expansion (on admission), edema-free (generally 2 days after the end of diuretic treatment), and moderate expansion. The last value was chosen arbitrarily to correspond with the maximal expansion obtained in the normal volunteers (see below). Diuretic treatment produced a significant fall in blood volume in the patients with moderate hypoproteinemia. In the patients with severe hypoproteinemia, the blood volume remained rather stationary. There was no difference in blood volume between the two subsets in the edema-free condition,

Table 1. Data of the nephrotic subjects at entry (maximal expansion), halfway during edema removal (moderate expansion), and after edema removal

	Group	A Edema-free	B Moderate expansion	C Maximal expansion	A-B	B-C	A-C
Mean arterial pressure, *mm Hg*	1	93.2 ± 2.3	95.7 ± 3.4	99.5 ± 3.2	—	—	q
	2	101.4 ± 3.3q	105.0 ± 2.4q	114.0 ± 4.6r	q	—	r
Creatinine clearance, *ml/min*	1	73.0 ± 8.5	79.7 ± 8.4	79.0 ± 9.7	q	q	q
	2	60.4 ± 7.2	65.2 ± 8.1	67.7 ± 9.3	q	—	q
Extracellular fluid volume, *liter/50 kg LBM*	1	14.7 ± 0.4	18.0 ± 0.8	24.1 ± 1.5	r	r	s
	2	14.7 ± 0.4	17.7 ± 0.3	23.6 ± 1.3	r	r	s
Blood volume, *liter/50 kg LBM*	1	4.3 ± 0.2	4.3 ± 0.2	4.5 ± 0.2	—	—	—
	2	4.5 ± 0.1	4.8 ± 0.1q	5.0 ± 0.1r	r	—	r
Plasma renin activity, *fmole AI/liter · sec*	1	2900 ± 1630	1450 ± 1050	950 ± 515	r	r	r
	2	1670 ± 1190	750 ± 1100	290 ± 50q	r	q	r
Plasma protein, *g/liter*	1	44.9 ± 2.7	40.6 ± 2.0	39.6 ± 1.5	—	—	—
	2	54.0 ± 1.6s	49.0 ± 2.2r	48.0 ± 1.8q	q	—	q
Plasma albumin, *g/liter*	1	14.6 ± 1.7	14.1 ± 1.1	13.1 ± 1.1	—	—	—
	2	22.4 ± 1.0s	19.1 ± 1.3r	17.3 ± 1.4s	r	—	r
Plasma colloid osmotic pressure, *mm Hg*	1	9.8 ± 0.2	9.0 ± 0.6	8.2 ± 0.4	—	—	—
	2	17.6 ± 0.6s	14.1 ± 1.1s	13.4 ± 1.0s	r	—	r
Proteinuria, *g/24 hr*	1	12.4 ± 1.7	14.1 ± 0.9	11.2 ± 1.0	—	—	—
	2	7.4 ± 1.6q	7.7 ± 1.5r	8.3 ± 1.2r	—	—	—

Values are means ± SEM and superscripted by q, r, and s when significant differences ($P < 0.05$, < 0.01, < 0.001, respectively) existed between Group 1 and Group 2. In the right-hand column, these symbols indicate significant differences within these groups between values found at the three hydration levels (A, B, and C).

Abbreviation: LBM, lean body mass.

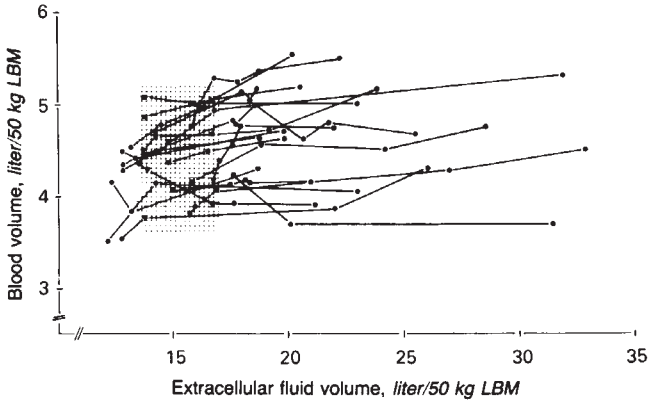

Fig. 1. *Relationship between extracellular fluid volume and blood volume during removal of edema in 21 patients with the nephrotic syndrome.* Values are expressed in liters/50 kg LBM (lean body mass). The *grid* demarcates values of these volumes estimated in normal volunteers on a liberal salt intake (mean + 2 SD, see **Methods**).

but the blood volume was significantly larger in Group 2 during moderate and maximal expansion. Nevertheless, in all patients, the changes in blood volume were small relative to the large changes in ECFV (Fig. 1).

The PRA showed a gradual rise during dehydration, and was significantly correlated with the ECFV when all observations were taken together: $r = -0.50$, $P << 0.0001$.

Plasma protein, albumin, and colloid osmotic pressure tended to rise during the treatment, significantly so in Group 2, while the proteinuria did not change.

Normal subjects

In eight cases, sodium balance was attained at all three sodium intake levels, the mean excretion being 22 ± 4, 202 ± 19, and 1052 ± 86 mEq/24 hr, respectively. One female subject did not achieve balance, but kept retaining sodium during the high-sodium diet, which was discontinued after 2 days. Because this group served as a reference for blood volume changes relative to total ECFV changes in the absence of hypoproteinemia, her data were included. Table 2 gives the data collected at both extremes of sodium intake. Although mean blood pressure was slightly higher during the sodium loading, the change was not significant. The creatinine clearance, ECFV, and blood volume rose, and PRA and PA fell significantly. When the observations made at all three sodium intake levels were pooled, significant negative correlations existed between PRA and ECFV (−0.82, $P << 0.0001$). Individual changes in blood volume and ECFV are depicted in Figure 2.

Table 2. Data of the normal volunteers at low and high sodium intake

Sodium intake/24 hr	20 mEq	1138 mEq	*P* value
Mean arterial pressure, *mm Hg*	88.4 ± 2.8	93.0 ± 2.0	NS
Creatinine clearance, *ml/min*	111.2 ± 6.0	137.9 ± 10.0	< 0.01
Extracellular fluid volume, *liter/50 kg LBM*	14.3 ± 0.3	17.2 ± 0.4	< 0.01
Blood volume, *liter/50 kg LBM*	4.5 ± 0.1	5.0 ± 0.2	< 0.01
Plasma renin activity, *fmole AI/liter · sec*	760 ± 130	35 ± 6	< 0.01

Abbreviation same as Table 1.

Comparison between NS patients and normal subjects

Mean arterial pressure in the NS patients exceeded that in the normal subjects. For Group 2, this difference was significant both when edema free and when moderately expanded ($P < 0.01$). Over the entire range of volume reduction, the mean fall in creatinine clearance was − 6.6 ± 4.1% in the patients against − 18.0 ± 4.6% in the normal volunteers ($P < 0.0001$). Relative to the changes in total ECFV, the alterations in blood volume

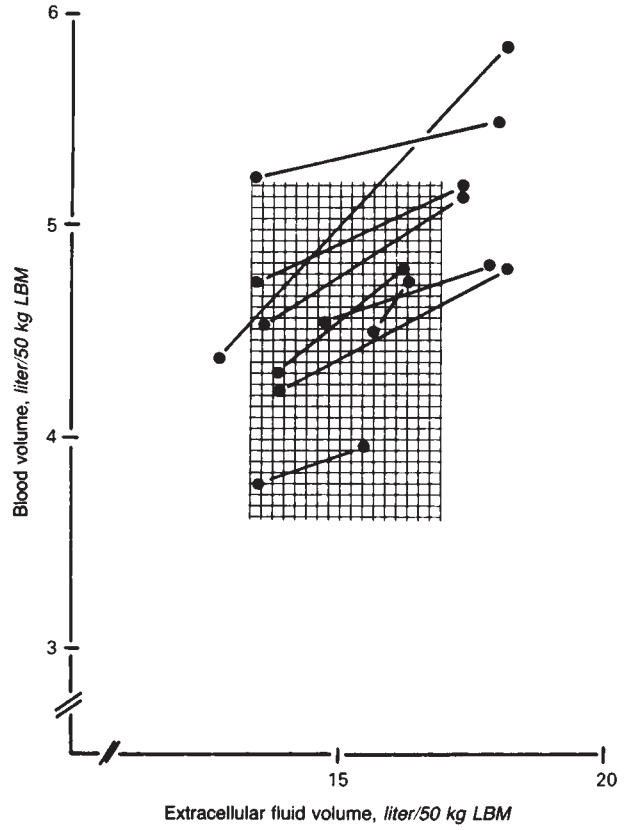

Fig. 2. *Relationship between extracellular fluid volume and blood volume in nine normal volunteers studied after equilibration at low (20 mEq) and high (1138 mEq) sodium intake.* Values are expressed in liters/50 kg LBM (lean body mass). This *grid* is an enlarged version of *grid* in **Fig. 1**.

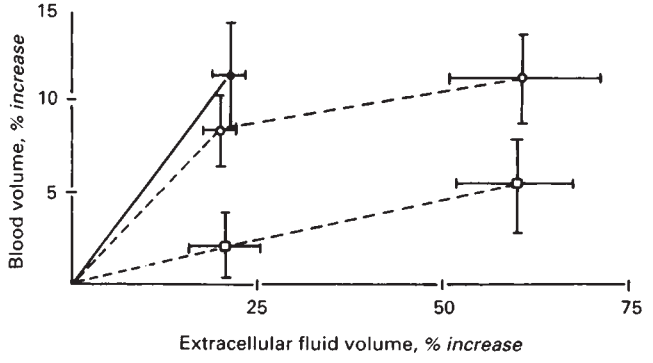

Fig. 3. *Relationship between extracellular fluid volume and blood volume as percentage of the volumes measured in dry conditions in nine normal subjects* (—— ●), *in 10 subjects with the nephrotic syndrome and severe hypoproteinemia* (Group 1, --- □), *and 11 nephrotic subjects with moderate hypoproteinemia* (Group 2, --- ○).

tended to be smaller in the patients. This is illustrated in Figure 3, where these changes are plotted as percentage of the baseline volumes (that is, the fluid volumes measured in the normal subjects when on a 20 mEq sodium diet and in the patients at the end of the diuretic treatment and the same diet). In the normal subjects, the sodium loading caused an 11.2 ± 3.0% rise in blood volume and a 21.4 ± 4.1% rise in ECFV; at the same

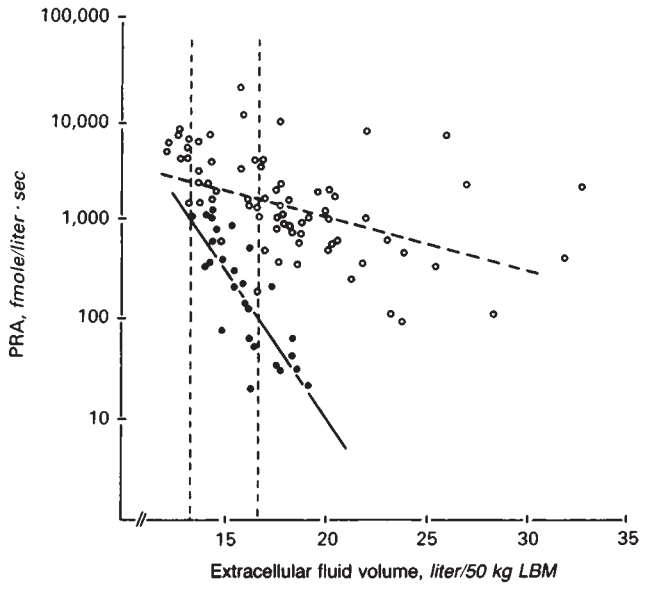

Fig. 4. *Relationship between extracellular fluid volume and plasma renin activity (PRA) in patients with the nephrotic syndrome* (○, 72 observations in 21 patients at different stages of edema removal) *and normal volunteers* (●, 27 observations in nine normals on three levels of sodium intake). Symbols are: ———, regression line for patients ($y = -0.0568\ x + 4.175$, $r = -0.50$, $P << 0.0001$); ------, regression line for the normal volunteers ($y = -0.304\ x + 7.087$, $r = -0.82$, $P << 0.0001$). The extracellular fluid volume is expressed as liter/50 kg LBM (lean body mass). The *vertical dotted lines* demarcate the normal area (mean ± 2 SD).

degree of ECFV expansion, the rise in blood volume was only 2.4 ± 1.9% in the NS patients of Group 1 ($P < 0.04$) and 8.1 ± 1.9% in Group 2 (NS). At maximal expansion, the blood volume exceeded the baseline value by 5.4 ± 2.6% in Group 1 and 11.0 ± 2.5% in Group 2, the excess in ECFV averaging 63.4 ± 8.4%.

After edema withdrawal, no difference existed between the mean blood volumes of Group 1 or of 2 and those of the normal subjects. At moderate expansion, the blood volume in the normals was larger than in the patients, the difference being significant only for Group 1 ($P < 0.05$). Figure 4 shows that there was a striking difference in the behavior of the PRA, which for all levels of ECFV were higher in the patients than in the normal controls. The regression lines for log PRA against ECFV are $y = -0.0568\ x + 4.175$ ($r = -0.50$, $P << 0.0001$) for the patients and $y = -0.304\ x + 7.087$ ($r = -0.82$, $P << 0.0001$) for the normal volunteers. Covariance analysis showed a significant difference both between intercepts and slopes ($P << 0.0001$).

Discussion

In the present study we have shown that excess fluid in patients with the NS can be withdrawn without production of functional hypovolemia: the blood pressure remains generally within a normal, often even mildly hypertensive range, and the decrease in renal function is only modest. The outstanding feature in our study undoubtedly concerns the blood volume behavior during extracellular volume expansion. In the normal volunteers expansion of the ECFV was accompanied by a substantial expansion of the blood volume, whereas in patients with severe hypoproteinemia, the blood volume appeared

rather constant, in spite of ECFV variations over an even larger range.

It was already known that, in normoproteinemic conditions, the blood volume can be very effectively expanded by salt loading [15], and that in normal humans infused saline, up to about 10% of the ECFV, spreads equally over the intravascular and extravascular compartment [16]. Manning and Guyton [17] reported recently that in overhydrated nephrectomized dogs an ECFV expansion of about 40% was accompanied by 25% expansion of the blood volume. Similar expansions of blood volume have been reported in patients with acute glomerulonephritis [18] and overexpanded postoperative patients [19]. The experiments done by Manning and Guyton [17] also demonstrated that the expansion of the blood volume is bound to an upper limit, because ECFV expansion beyond 40% did not result in further increase in blood volume. On this item, no comparable data are available in humans, and we also did not attain such a degree of expansion in the normal subjects. In the nephrotic subjects, however, the mean increase in ECFV on admission exceeded this point (Fig. 3). Nevertheless, the increase in blood volume remained far below the reported maximal increase of 25%, being only 11% in the patients with moderate hypoproteinemia and 5% in the group with severe hypoproteinemia. Thus, contrary to what would happen in normal subjects, in the NS patients, retained salt and water was preferentially localized in the interstitium, and, conversely, diuretic treatment had relatively little influence on the intravascular volume. Particularly in those patients with very severe hypoproteinemia, the curve relating blood volume to the ECFV runs very flat (Fig. 3). According to our data, patients with minimal lesions NS will often belong to this subset.

The reasons for this preferential distribution of retained fluid to the interstitium were not investigated in the present study. It may be related to the fact that in the NS (and other types of protein depletion) a reduction in tissue-fluid protein concentration and colloid osmotic pressure takes place parallel to the change in the blood [8–11]. Indeed, very low levels of tissue-fluid colloid osmotic pressure approximating zero may arise during severe hypoproteinemia [8, 9, 11]. In such conditions, interstitial fluid expansion may not result in the reduction of the pericapillary colloid osmotic pressure that in the normal situation would have forced some of the excess fluid within the vessels. Guyton, Taylor, and Granger [15] have theorized that the reduction of tissue fluid colloid osmotic pressure following interstitial fluid expansion occurs in association with a rise in tissue fluid hydrostatic pressure and lymph flow, and that these factors together form an "edema-preventing mechanism". In case of hypoproteinemia, the term "blood-volume-preserving mechanism" seems more appropriate, because without these factors the blood volume would probably have fallen below normal, certainly so in the edema-free state.

It may be questioned whether these homeostatic mechanisms have entirely succeeded to preserve the blood volume, because this tended to be lower in the edema-free nephrotics of Group 1 than in the normal subjects receiving a salt-poor diet. The difference was, however, small and not significant. Because cardiopulmonary blood volume and the filling pressures of the heart rather than absolute blood volume values are relevant to the circulatory homeostasis, it is helpful to consider other circulatory variables for evidence of existing "hypovolemia". The blood pressure was generally (in Group 2 even significantly) higher than in the normal subjects, regardless of the degree of expansion. Orthostatic hypotension was only observed in two patients in whom factors other than hypovolemia were probably responsible for the hypotension. We cannot explain why orthostatic hypotension occurred more often in another study of nephrotic subjects treated with diuretics [6].

In another large series of patients with the NS reported previously, we also noticed a tendency to an increased rather than a decreased blood pressure, which we have attributed to the uniformly present fluid retention [20]. The present study shows that this tendency persists under edema-free conditions. This suggests that additional factors like the renin-angiotensin-aldosterone system must play a role. In view of the elevated blood pressure level, this system was inappropriately stimulated in the NS patients relative to their state of hydration (Fig. 4). The curve relating renin to ECFV was also significantly different, that is, much flatter in the patient group, suggesting that the volume retention suppressed the PRA insufficiently to prevent a rise in blood pressure. The finding of others [21, 22] that elevated renin levels in patients with the NS were unaffected by changes in sodium intake also point to inappropriate renin stimulation. The mechanism underlying this PRA stimulation is obscure. Factors such as a low plasma oncotic pressure [23] and a low solute delivery to the macula densa due to an increased proximal tubular reabsorption [24, 25] may play a role.

Edema removal was followed consistently by a reduction in creatinine clearance, which was modest compared to the changes observed in the normal volunteers. Lowenstein, Schacht, and Baldwin [7] even reported an increase in creatinine clearance during volume removal in nephrotic subjects, a phenomenon not encountered in the present study. Their observations do, however, support our contention that nephrotic patients generally do not become hypovolemic when made edema free.

In summary, gradual removal of edema in patients with the NS was not followed by functional hypovolemia, even in those subjects with a very low plasma colloid osmotic pressure. Their blood volumes, although less than in normal subjects at similar degrees of ECFV expansion, were not below normal in the edema-free state. Postural hypotension occurring twice could be attributed to other causes, and the blood pressure was often modestly elevated. The elevated renin occurring in spite of this increased blood pressure suggests a primary renal disturbance of renin release rather than stimulation due to hypovolemia.

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