Observations on Edema Formation in the Nephrotic Syndrome in Adults with Minimal Lesions

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Ten adult patients with the nephrotic syndrome and minimal lesions on renal biopsy were studied while receiving a salt poor diet before and after 13 prednisone-induced remissions.

They were selected because the finding of a slight to moderate increase in blood volume in all of them and of an elevated blood pressure level in some of them was at variance with the expected hypovolemia.

After remission, blood pressure decreased in 12 and plasma volume in 10 patients, whereas plasma renin activity (PRA) increased in eight and decreased in three patients. Creatinine clearance, which had been severely depressed in four subjects, increased in all, whereas radioactive chromium sulfate (^{51}Cr) EDTA clearance increased in six of seven instances. In contrast, renal plasma flow (^{125}I-hippurate clearance) was normal or increased in the nephrotic phase and decreased in five of seven cases, resulting in an increase towards normal of the very low filtration fraction.

These results lend no support to the conventional concept that hypovolemia is the main factor responsible for the maintenance of edema in this condition and suggest that other factors, such as impaired glomerular permeability, may be important.

Although no combined measurements of these hemodynamic parameters have been reported in a similar group of patients, many data from the literature suggest that some degree of hypervolemia is a common finding in adults with an established nephrotic syndrome.

Edema formation in patients with renal disease can be due to either an inability of the diseased kidney to excrete salt and water or be the result of a normal response of the kidney to excessive demands of physiologic volume regulation. A prototype of the former disturbance is found in acute glomerulonephritis, in which primary impairment of glomerular filtration results in expansion of the extra- and intravascular fluid volumes, which leads to such signs as hypertension, increased venous pressure and congestive heart failure.

The latter situation is assumed to occur in the nephrotic syndrome, in which glomerular leakage of protein causes a state of hypovolemia, which in turn induces a successful but inappropriate response of the otherwise relatively normal kidney, leading it to retain fluids. Consequently, this condition is characterized by low plasma and blood volumes, absence of hypertension and increase in renin activity and aldosterone production or an elevation in plasma levels. Several investigators have, however, reported the frequent occurrence of normal or increased plasma and blood volumes [1-4], hypertension [5], and

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TABLE I Some Data of the Patients During a Period of Heavy Proteinuria and Edema and After Recovery

Case No.	Age (yr) and Sex	Blood Pressure (mm Hg)		Serum Albumin (g/100 ml)		Creatinine Clearance (ml/min)		PRA Supine (ng AI/100 ml/hour)		Blood Volume (liters)	
		N	R	N	R	N	R	N	R	N	R
1	18, M	140/ 90	130/ 80	2.6	5.2	110	151	145	295	5.4	5.2
2	40, M	160/ 90	120/ 60	1.7	4.5	34	127	125	295	7.2	6.2
3	20, M	125/ 90	120/ 70	1.4	4.9	66	91	405	145	5.6	5.0
4a	22, F	140/ 80	123/ 75	1.3	4.0	50	90	175	205	4.6	4.4
4b	25	120/ 80	125/ 75	1.5	3.2	40	96	320	60	4.8	4.4
5	64, M	150/ 90	130/ 80	1.8	3.6	85	85	105	390	5.1	4.8
6	26, M	130/ 90	120/ 80	0.9	3.3	67	135	315	580	5.1	4.9
7a	19, M	180/120	150/100	1.2	3.1	120	170	355	500	6.3	4.8
7b	21	165/ 95	140/ 70	1.8	3.3	100	124	60	185	6.3	6.0
8a	29, M	140/100	125/ 85	1.4	3.3	80	84	315	350	5.5	5.3
8b	30	135/ 90	132/ 85	1.6	3.5	113	135	85	. . .	6.6	6.4
9	23, M	150/ 95	135/ 90	1.9	3.3	109	143	. . .	. . .	6.1	5.8
10	56, M	135/ 95	105/ 80	1.4	3.2	18	104	510	145	5.6	5.3

NOTE: a and b refer to first and second nephrotic phase; N = during nephrotic phase, R = during remission; PRA = plasma renin activity (normal values with this diet; 100 to 370 ng/100 ml/hour).

normal or low plasma renin and aldosterone concentration [6].

We selected a series of adult patients with "minimal-lesion nephrotic syndrome" in whom a normal or increased blood volume had been found in order to analyze the factors responsible for salt retention in this condition. These patients offered the additional advantage that they could also be investigated after (steroid-induced) recovery, so that each patient served as his own control, thus obviating the problem of interindividual variations of normal values. Our results show that the conventional conception of edema formation in the nephrotic syndrome is not generally valid, even in patients with "minimal lesions."

PATIENTS AND METHODS

Ten adult patients (one woman and nine men) without light microscopic or immunofluorescence abnormalities in renal biopsy specimens were studied after several days of equilibration in the hospital without medication and while adhering to a salt-poor (20 meq sodium/day) diet. None of them had recently been treated with prednisone. Diuretic therapy that had been given to some of them was discontinued at least one week before the studies. Three of the patients were studied another time during and after a relapse of the syndrome, giving a total of 13 paired observations.

The investigations were performed before the start of prednisone therapy with the patient in the recumbent position in the morning after a light breakfast. Plasma volume was determined by the radioiodinated human serum albumin dilution method after 10 minutes of equilibration. Blood volume was calculated from hematocrit value and plasma volume assuming a total body hematocrit value of 0.91 times the venous hematocrit value. Plasma renin activity (PRA) was measured with a modified Haber method [7]. Blood pressure was taken as the mean value of at least three readings by sphygmomanometer during the same day.

Twenty-four hour creatinine clearance was determined on the preceding day. On another day, the renal plasma flow and glomerular filtration rate (GFR) were determined simultaneously during the infusion of ^{125}I-hippurate and ^{51}Cr EDTA, using the method with urine collection.

These determinations were repeated under the same conditions, including salt restriction, one half to six months after a complete remission had been obtained by prednisone therapy. Most patients (except in Case 1, 2, 3, 4a and 9) were still receiving steroids during the control studies.

Statistical analysis was performed using the Wilcoxons' test for paired data.

RESULTS

Clinical Condition. Some of the initial individual findings are given in **Table I.** All subjects were grossly edematous and excreted minimal amounts of sodium during the first study, whereas body weight decreased 4 to 26 kg after recovery. Serum albumin concentrations were low in all subjects (mean 1.58 g/100 ml) and reached normal values (mean 3.67 g/100 ml) during remission (**Figure 1**).

Blood Pressure and Volume Changes (Figure 1). Blood pressure was increased (>150/90 mm Hg) during the nephrotic phase in five cases and was lower after remission in 12 of the 13 episodes, including those in cases in which blood pressure values were within the normal range. The mean systolic and diastolic pressures in the entire group were significantly higher (17 and 14 mm Hg, respectively) than after recovery.

Plasma volume and blood volume during the edematous phase were approximately normal or increased and showed a mean significant decrease of 0.3 and 0.3 L, respectively, after remission.

Renal Hemodynamics (Figure 2). Creatinine clearance was depressed in seven patients and returned to normal during remission. In 12 of 13 observations, an increase was noted after recovery; the mean increase for the group (42 ml/min, or 56 per cent) was highly significant.

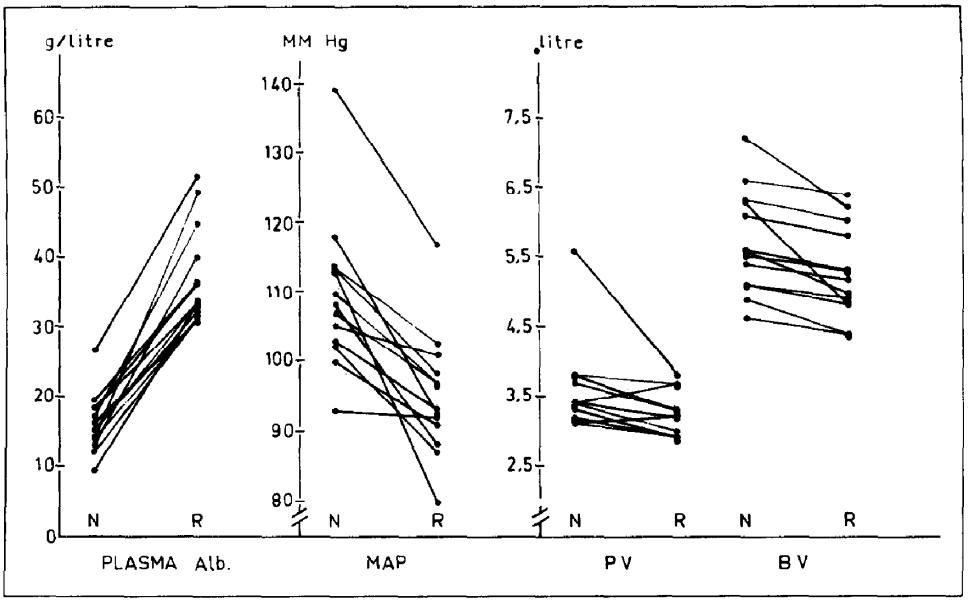

Figure 1. Values of plasma albumin (Plasma Alb) concentration, mean arterial pressure (MAP), plasma volume (PV) and blood volume (BV). Lines connect the data of individual patients during the nephrotic phase (N) and after remission (R). Significance levels of differences between N and R: plasma albumin and MAP $p < 0.0001$, PV $p < 0.02$ and BV $p < 0.001$.

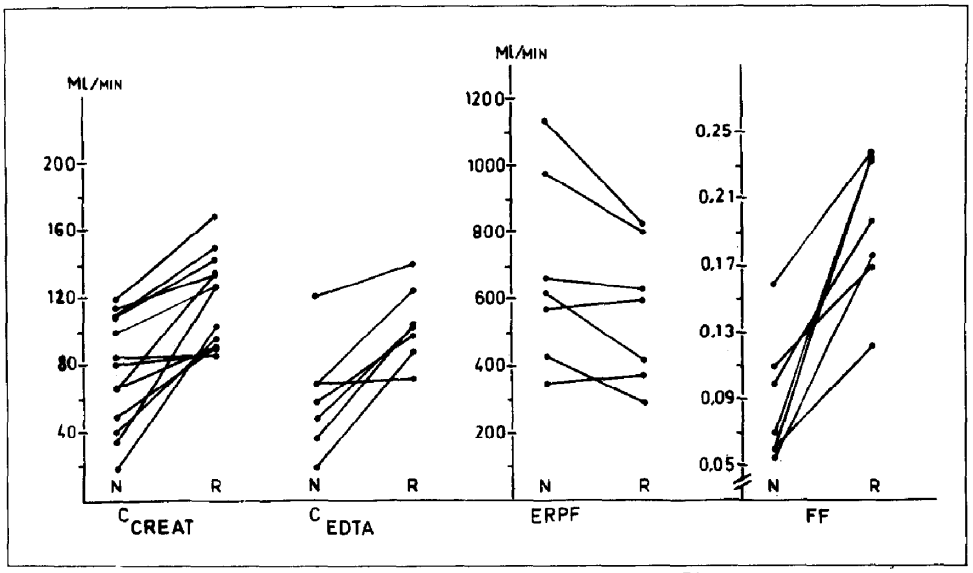

Figure 2. Individual values of 24-hour creatinine clearance (C_{creat}), ^{51}Cr-labeled EDTA clearance (C_{EDTA}) and effective renal plasma flow (ERPF) determined by ^{125}J-labeled hippurate and filtration fraction (FF). Significance levels of differences between N and R: C_{creat} $p < 0.0001$, GFR and FF $p < 0.02$ and ERPF $p < 0.06$.

In seven patients we also determined the GFR and renal plasma flow. A similar increase in GFR (from 60 to 104 ml/min) was observed after recovery. Renal plasma flow was within normal limits during the nephrotic phase, resulting in a very low filtration fraction (mean 0.088) which significantly increased to 0.198 after remission. It is noteworthy that in five patients renal plasma flow was higher in the edematous state than after recovery.

Plasma Renin Activity (Figure 3). The logarithms of PRA values before remission were within or below the range to be expected under salt restriction. After remission, a decrease of the value during recumbency and upright position was found in three and four patients,

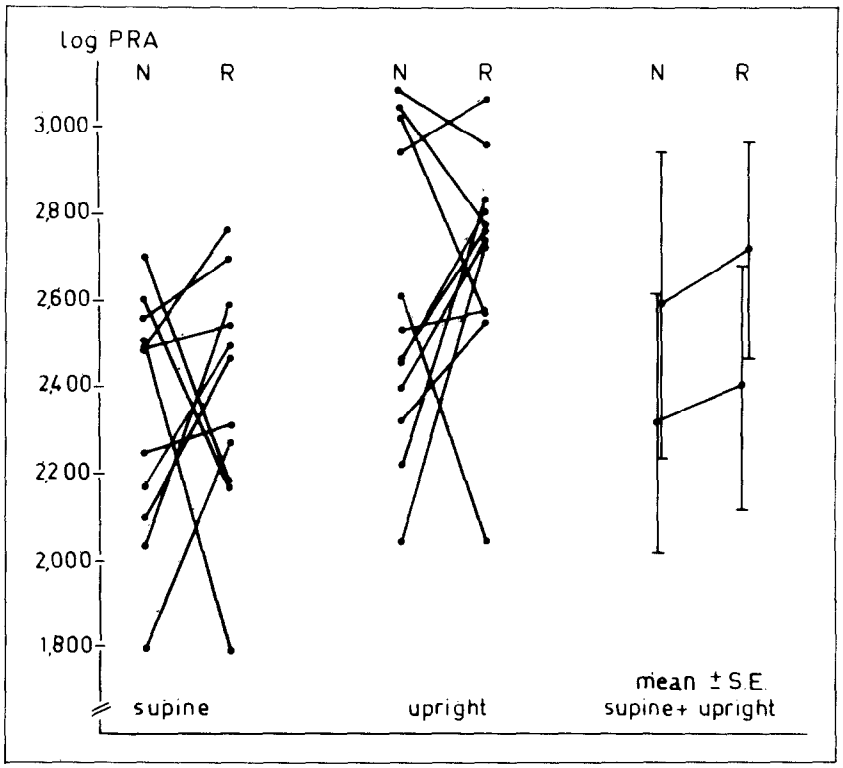

Figure 3. Logarithms of plasma renin activity (PRA, ngAI/100 ml/hr) of individual patients as well as mean values for the group. The differences were not significant ($p > 0.1$).

respectively, whereas the others showed an increase. This resulted in a slight, but not significant, increase in the mean values for the group, despite the fact that the mean sodium excretion during the nephrotic phase was lower (14 meq/day) than after recovery (36 meq/day).

Interrelations of the Measured Parameters. As reported by us previously [2], no clear relationship could be found between the changes in blood volume and blood pressure, and no correlations were found between the plasma albumin level, the degree of renal functional impairment, blood pressure and PRA. It is of note that the three patients (Cases 2, 4 and 10) whose renal function was most severely compromised had high blood volume values (+1.0, +0.2 and +0.3 liter) and that the blood pressures were 160/90, 140/80 and 135/95 mm Hg, respectively.

The assumption of low plasma and blood volumes in the nephrotic syndrome is a logical consequence of Starling's concept and seems to offer a satisfactory explanation for the often highly resistant fluid retention in patients with morphologically and functionally intact kidneys. The experimental evidence is, however, equivocal. Many investigators, although confirming the presence of decreased blood volume in some patients, nevertheless remark that it was less severe and less frequent than expected [8–11].

What is more important is that in none of the reported studies could a relationship be found between the degree of plasma volume lowering and plasma albumin level [5]. From **Table II,** which gives a survey of the relevant data of nine studies, it is clear that, regardless of the method used, normal or even increased blood volume values are the rule rather than the exception, although there are marked differences between the different series. Particularly interesting is the report of Oliver [12] who, like us, compared the same patients before and after remission; in only four of 22 cases did the patient show an increase in plasma volume after the disappearance of the nephrotic syndrome.

These observations leave no doubt, in our opinion, that in the nephrotic syndrome the plasma volume and blood volume are maintained close to normality and may even be increased despite the marked decrease in colloid osmotic pressure. The strength of the forces counteracting the passage of fluid from the blood stream is, of course, demonstrated by the fact that a steady state without any further decrease in blood volume is eventually reached in all nephrotic subjects, even in those with colloid osmotic pressure values only one third of normal. It was shown as early as 1942 by Warren et al. [14] that the decrease in plasma volume after experimental depletion of serum proteins can be prevented by massive extracellular fluid expansion. Likewise, similar expansion in normal animals leads to large increases in the intravascular volume [15]. The plasma volumes in nephrotic patients are certainly lower than

TABLE II Blood Volume in the Nephrotic Syndrome as Reported in the Literature in Order of Publication

Reference	Method	No. of Patients with Blood Volume in Percentage of Normal Value		
		<−10%	−10%–+10%	>10%
Squire [8]	Evans blue		5 PV ± 25% decrease	
Metcoff, Janaway* [10]	Evans blue		mean PV −10% 7 children	
Yamauchi, Hopper [11]	^{51}Cr-ery	40	22	10
Oliver* [12]	RISA	9	10	3
Garnet, Webber [13]	RISA	7	3	5
Jensen et al. [3]	RISA	2	20	8
Eisenberg [1]	^{51}Cr-ery	3	10	2
Hopper et al.* [5]	^{51}Cr-ery	19	22	1
Kelch et al.* [4]	^{51}Cr-ery	...	5	1
Meltzer et al. [6]		3	12	...
Total		83	104	30

NOTE: RISA = radioiodine labeled serum albumin; ^{51}Cr-ery = ^{51}chromium tagged erythrocytes; PV = data only on plasma volume.
* Reports only on "minimal change" glomerulopathy.

they would have been with higher albumin levels, as illustrated by the fact that albumin infusions lead to large increases [16] and, occasionally, to circulatory overload [9,17].

Of interest in this respect are observations in subjects with congenital analbuminemia who have normal blood volumes and very little or no edema [18]. One of the reasons for the maintenance of the circulating volume may be the greatly enhanced lymph flow [19]. After removal of excess extracellular fluid by vigorous saliuretic treatment, the plasma volume is also lowered in patients with the nephrotic syndrome [13]. This may be one reason for the low values that have been found more frequently in some reports.

Hypertension. The frequent occurrence of moderate degrees of blood pressure increases in patients with the nephrotic syndrome is difficult to reconcile with the concept of a decreased blood volume. Yet 11 investigators reporting on blood pressure found it frequently increased also in patients with minimal lesion nephropathy (see **Table III**). In the present investigation we not only confirmed these observations but even found a blood pressure decrease in all but one subject after remission. As in our previous study [2], no clear relationship with blood volume was found.

Renal Functions. Like hypertension, decreased renal function is not considered to be a feature of the "pure" nephrotic syndrome with minimal lesions. However, all investigators mention the frequent occurrence of a transient decrease in the GFR (Table III). Hopper et al. [5] found decreased creatinine clearances in 18 of 31 adult patients but no relationship with changes in blood pressure or blood volume.

Of particular practical importance is the question whether decreases in filtration rate are due to hypovolemia. This possibility is suggested by the increase in GFR and salt excretion that can be induced in these patients by the infusion of hyperosmotic salt-poor albumin [17]. Most of the investigators who used this or dextran treatment, however, have reported that in about 50 per cent of the patients the GFR does not increase and diuresis does not occur despite the infusion of amounts large enough to raise the blood volume well above normal values [8,9,16,22–24]. A few cases of minimal lesion nephrotic syndrome have been described in which reversible renal failure, necessitating dialysis treatment, occurred [17,24]. However, since the investigators state that some of these patients had increased blood pressure and no signs of hypovolemia, the suggestion that these cases were due to extreme decreases in blood volume seems unwarranted.

It is generally recognized that the renal blood flow is often normal in minimal lesion nephrotic syndrome, resulting in a marked decrease in filtration fraction [22,25,26]. After remission, the filtration fraction increases as a result of an increase in GFR, whereas the renal plasma flow remains constant or even decreases [30]. The low filtration fraction during the hypopro-

TABLE III Frequency of Hypertension and Decreased GFR in Patients with Minimal Lesion Nephrotic Syndrome, as Reported in the Literature

Reference	Hypertension (% of patients)	GFR Decrease (% of patients)	Remarks
Metcoff, Janaway [10]	10–50	50	No relation to prognosis
Churg [20]	40	30	...
Hopper et al. [5]	30	60	No relationship with blood volume
Cameron [21]	30	70	Adults only

TABLE IV **Plasma Renin Activity (PRA) and Aldosterone Excretion (UA) or Plasma Concentration (PA) in Patients with the Nephrotic Syndrome, as Reported in the Literature**

Reference	PRA (no.)		UA or PA (no.)		Remarks
	Normal or Low	Increased	Normal or Low	Increased	
Imai [31]	2	4	...	...	3 increased and 3 decreased after recovery
Oliver, Awings [23]	...	...	...	8	No relation to plasma volume
Kleinknecht, Maxwell [35]	4	11	...	...	...
Oelkers [32]	4	3	...	...	...
Pessina et al. [33]	1	4	...	...	...
Medina et al.* [30]	3	6	2	7	...
Meltzer et al. [6]	12	3	12	3	...
Chonko et al. [34]	2	8	2	8	...

* This investigator measured plasma renin concentration and found angiotensin II levels normal in all patients, but renin substrate often reduced.

teinemic phase and the decrease in renal plasma flow after remission are not consistent with a state of hypovolemia. The very low oncotic pressure would rather favor a high filtration fraction, which was indeed found in a patient with analbuminemia [27] whose filtration fraction decreased from 0.38 to 0.23 after the infusion of albumin. In experimental nephrotoxic serum nephritis in rats, the GFR is preserved or slightly depressed, whereas the glomerular permeability coefficient is greatly decreased [28,29], filtration being maintained by an increase in elevation of the mean capillary pressure without reaching filtration equilibrium. On the basis of polyvinylpyrrolidone clearances, Robson et al. [26] reported decreases to less than 20 per cent of normal in the clearance of molecules smaller than 40 Å in children with minimal lesion nephrotic syndrome. As in the present study, inulin clearances were about 25 per cent higher during remission, and the renal plasma flow decreased slightly. These workers interprete their findings as indicating a primary impairment of glomerular filtration, probably as a result of the fusing of foot processes. Whether decreased glomerular permeability by itself can result in edema formation, and what role must be assigned to increased tubular reabsorption, cannot be decided on the basis of these clinical investigations.

Renin and Aldosterone. Systematic investigations on plasma renin and aldosterone levels are surprisingly scarce in the literature, and the available data are difficult to interpret in view of the marked influence of the sodium balance [30]. Variable increases in PRA have been reported [31-33]. Review of some of these data (**Table IV**) leads to the conclusion that a certain stimulation of the renin-angiotensin-aldosterone axis is present only in some patients with the nephrotic syndrome. Medina et al. [30] compared the plasma renin and aldosterone levels in patients with the nephrotic syndrome partaking a standardized sodium-restricted diet. Only one of their patients had minimal lesion nephrotic syndrome. Plasma renin concentration was increased in six of nine determinations, but the angiotensin II levels lay within the normal range. Plasma aldosterone was only moderately increased with the subject supine but normal with the subject in the upright position. In a recent study [6], normal to low PRA and aldosterone levels were found in the nephrotic phase, and a rise in three cases after recovery. Chonko et al. [34] studied eight patients (but none with minimal lesions) during both low and high sodium intake. The PRA and aldosterone levels decreased after sodium loading in only two of the eight subjects. These workers conclude that "other factors than elevated plasma aldosterone must be involved in the edema formation of these patients."

We found that under severe salt restriction the PRA is on average lower during the edematous phase than after recovery. In three cases it was definitely depressed. Our findings are not directly comparable with those in the literature referred to, because of differences in the underlying disease, the sodium balance and the technique used for renin determination. They are, however, in fair agreement with the over-all impression that plasma renin is relatively increased in most, but not all, patients with the nephrotic syndrome but not to such a degree that it indicates the consistent presence of hypovolemia.

The present patients were selected on the basis of increased blood volumes, and the results do not permit conclusions as to the proportion of patients behaving in the way described here, but our impression is that among adults this is the rule rather than the exception. We, therefore, conclude that our findings concerning the blood pressure, renal hemodynamics, blood volume and PRA during the nephrotic state and after remission do not support the concept that hypovolemia is mainly responsible for the development and persistance of edema in adult patients with minimal lesion nephrotic syndrome. The lack of a consistent relationship between these parameters and sodium excretion, in agreement with the pertinent literature, also argues against the concept that changes in blood pressure, PRA and renal function are dependent on changes in blood volume. A variable degree of impairment of glomerular permeability would be compatible with these observations.

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