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Atrial natriuretic factor in the acute nephritic and nephrotic syndromes

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Atrial natriuretic factor in the acute nephritic and nephrotic syndromes. Because the role of systemic hormones in the pathophysiology of edema in acute renal disease remains incompletely understood, we compared the levels of atrial natriuretic factor (ANF) and plasma renin activity (PRA) in patients with acute glomerulonephritis (AGN), nephrotic syndrome (NS), and normal individuals during salt deprivation and salt loading. Sixteen patients with AGN (10 males) and nine patients with NS and hypoalbuminemia (7 males) were studied on admission, and after recovery (12 AGN patients) or remission (4 NS patients). Eighteen normal controls were each studied after five days on a low (20 mEq Na/day), regular (120 mEq Na/day) and high (300 mEq Na/day) dietary salt intake. Patients with AGN and NS had comparable edema (AGN 2.8 ± 0.53 kg; NS 3.36 ± 0.47 kg; SE) and urinary Na excretion (mean ± SEM: AGN 0.97 ± 0.11 mEq/hr; NS 1.06 ± 0.16 mEq/hr), but AGN patients had five times higher ANF (AGN 27.2 ± 4.06 fmol/ml; NS 5.51 ± 1.02 fmol/ml; $P < 0.001$) and six times lower PRA ng/liter · sec levels (AGN 0.187 ± 0.047; NS 1.144 ± 0.222; $P < 0.001$) than NS patients. The degree of edema was correlated with ANF levels in AGN patients ($P < 0.001$) but not in NS patients. There was a strong exponential negative correlation ($r = -0.773$, $P < 0.0001$) between ANF and PRA, in which AGN patients and Na-restricted controls were located in the opposite ends of the volume sensing-response, and NS patients in the middle, alongside controls with regular Na intake. Our studies suggest that intrarenal mechanisms are responsible for Na retention in AGN as well as in NS, but AGN patients have a compensatory hormonal response related to the degree of fluid retention, while volume-sensing receptors in hypoalbuminemic NS patients are neither actively stimulated nor suppressed, probably due to increased transudation of fluid out of the capillaries.

Evaluation of volume sensing hormones is a useful approach to understand the pathophysiology of renal conditions characterized by sodium retention and edema. When edema results from an intrarenal defect causing impaired sodium excretion, as in acute glomerulonephritis, the hormonal systems show a compensatory response triggered by, and directed to correct, an expanded plasma volume. In contrast, when the hormonal changes reflect a contracted intravascular compartment, it is assumed that the kidney is responding appropriately to a homeostatic need with sodium retention. The latter situation was thought to be characteristic of the nephrotic syndrome, in which hypoalbuminemia could be the driving force of the transudation of fluid out of the capillaries. However, this attractive explanation was not substantiated in several studies that showed significant variability and normal mean levels of plasma renin activity [1–5] and atrial natriuretic factor [6, 7] in nephrotic patients.

Further insight into these issues could be gained, in our opinion, by comparing patients with acute glomerulonephritis and patients with nephrotic syndrome, with control individuals under sodium restriction as well as sodium loading. The two patient groups should offer a pathophysiological contrast, and the normals, on low and high salt diets, should encompass the limits of a physiologic hormonal response. This paper reports such an investigation with respect to atrial natriuretic factor and plasma renin activity.

Methods

Patients

Studies were done in 16 patients with acute glomerulonephritis (AGN), and 9 patients with nephrotic syndrome (NS).

Patients with AGN, 10 males and 6 females, ranged in age from 2 to 19 years. Thirteen of them had poststreptococcal etiology. These patients were studied upon admission and 12 of them were studied again 5 to 10 days later, after diuresis had occurred. Eight patients had repeated evaluation, including ANF determinations, 4 four 12 weeks after discharge. The initial studies were done at the time of admission before any medication was given, or in three cases, after more than four hours had elapsed from a dose of furosemide (20 mg intravenously) given before admission. During hospitalization, antihypertensive treatment and loop diuretics were given in the first few days as dictated by the clinical conditions, but all medications had been discontinued at least three days before the time when the studies in the convalescence period were done. Low salt diet (20 mEq Na per day) was followed by these patients throughout their hospitalization, including at the time of the postacute studies.

Patients with NS (7 males, 2 females) ranged in age from 8 to 18 years. They were diagnosed as having membranoproliferative glomerulonephritis (2 patients), membranous glomerulonephritis (2 patients, one of them due to lupus erythematosus), minimal change disease (1 patient), poststreptococcal glomeru-

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lonephritis (1 patient), and steroid-responsive nephrotic syndrome, presumed to be minimal change disease (no biopsy was done, in 3 patients). These patients had the full spectrum of the nephrotic syndrome, including proteinuria ranging from 4.1 to 7.2 g/day, and hypoalbuminemia ranging from 1.8 to 2.4 g/dl. They were studied within 48 hours of admission, before a definite diagnosis was established. None was receiving steroids at that time. They were prescribed a sodium restricted diet, similar to that of the patients with AGN, and had not received diuretic medication for at least eight hours before studies were done. At a later time, patients with NS were evaluated to decide which patients had remission and did not require continued medication; this was the case in three patients with minimal change disease and one patient with poststreptococcal etiology. These four patients had repeated studies after remission of NS three to eight weeks after the initial studies.

All patients had a complete physical examination, blood pressure determinations by at least two observers, and their weight was determined by the same person (DC) at the same time of the day and with the same clinical equipment to a discrimination of 0.1 kg. Supervised urinary collections of one to four hours were obtained in the patients at the time of admission because diuretic therapy could not be postponed for longer time, and 24-hour urine collections were done after recovery for determination of sodium and creatinine excretion. Blood for atrial natriuretic factor (ANF) and plasma renin activity (PRA) determination was drawn in the sitting or semi-recumbent position after 30 minutes of rest in every occasion.

Controls

Eighteen normal individuals (10 males), ranging in age from 4 to 22 years (median 16 years) were used as control group. They were apparently healthy and had a normal physical examination. Their serum hemoglobin, albumin, creatinine and urine analysis were also normal. Each of them was studied during three isocaloric sodium intakes: low (20 mEq Na per day), normal (120 to 150 mEq Na per day) and high (300 mEq Na per day). The high sodium diet required supplementation with NaCl in prepared capsules. Blood pressure and weight were determined daily in the morning. Compliance with the prescribed diet was tested by determination of 24-hour urinary sodium excretion. Studies were done after five days on the corresponding diet when blood was drawn at 8 a.m. after 30 minutes of rest in the sitting position for determination of ANF and PRA.

Laboratory determinations

Plasma levels of immunoreactive ANF (i-ANF) were determined in 6 ml blood as described previously [8]. Samples were obtained in ice-chilled tubes containing 1 mg ethylenediaminetetra acetate, 10 μl methanesulphonyl fluoride (10 to 3 mol/liter), and 10 μl pepstatin A (500 μmol/liter), per ml of blood to prevent degradation of ANF. Samples were immediately spun for 20 minutes at 4°C and stored at −70°C until assayed. Specific radioimmunoassay was used to determine i-ANF [9] after extraction with Sep-Pak cartridges (Waters Associates, Milford, Massachusetts, USA) as described before [10]. Sensitivity of the assay was 0.29 fmol/ml, and i-ANF levels were not corrected for recovery, which was 80 to 94% [8].

Plasma renin activity was determined as described previously [11] with commercially available radioimmunokits (SB-REN-1, Compagnie Oris Industrie S.A., Gif sur Ivette, France). Urinary and serum electrolytes were determined by flamephotometry and serum albumin and blood chemistries by autoanalyzer methodology.

Cardiovascular status

A complete physical examination, (including evaluation of breathing, neck veins, lungs and heart) routine laboratory test, creatinine clearances and chest X-rays were done in all patients. Mean arterial pressure (MAP) was calculated as:

$$MAP = \frac{(\text{systolic} + 2\ \text{diastolic})}{3}$$

Edema was calculated by subtracting the edema free weight found after recovery from the admission weight. Weight changes in the control group were noted as the difference in weight between the first and last day of the corresponding sodium diet.

Non-invasive assessment of cardiac output and stroke volume by echocardiography was done in five patients with AGN (patients AGN 2, 3, 6, 8, 10 in Table 1) and one patient with NS (NS 9 in Table 2).

Statistical methods

Results are expressed as mean ± SEM or SD, as indicated. Statistical differences were calculated by independent or paired samples t-test, as well as by non-parametric methods (Wilcoxon's rank sum and signed rank test). Correlations were calculated by parametric (Pearson's correlation) and non-parametric (Spearman's correlation) methods. P values were similar with both statistical approaches and the values of parametric methods are used in the text. Results were considered significant if two-tailed P values were <0.05. Statistical analysis was done with the help of a commercially available, statistical computer package (Statgraphics®, STSC Inc., Rockville, Maryland, USA).

Results

Table 1 shows the individual patients' data. Patients with AGN had ANF values ranging from 4.9 fmol/ml to 52.3 fmol/ml. In contrast, patients with the NS who had comparable degree of edema and similar urinary sodium excretion had mean values of ANF and PRA that were five times lower and six times higher, respectively, than the values found in patients with the acute nephritic syndrome (Table 1). The creatinine clearance (ml/min corrected for 1.73 m^2 surface area; mean ± SEM) of patients with AGN was 55 ± 4.63, and in patients with the NS it was 77.9 ± 11.55 ($P < 0.01$, Table 1). No significant correlation was found between ANF levels and the creatinine clearance; however, AGN patients 2, 6 and 10 had values of 30 to 40 ml/min (Table 1).

Patients with AGN showed evidence of intravascular overload that, in general, correlated with the degree of edema and hypertension (Table 1). Patients AGN2, AGN7 and AGN10 had tachypnea, orthopnea, distended neck veins and a tender liver 3 to 4 cm below the costal margin. The chest X-ray taken on admission showed cardiomegaly in patient AGN6 and parahilar pulmonary vascular engorgment which disappeared after diuresis (as determined by comparison with another chest X-ray

Table 1. Patients' data

Patient (*Age, sex*)	Diagnosis	Blood pressure *mm Hg*	Edema *kg*	C_{Cr} *ml/min*	Urinary sodium *μEq/min*	PRA *ng/liter · sec*	ANF *fmol/ml*
AGN1 (13,M)	PSGN	165/110	1.5	60.5	20.8	0.089	23.9
AGN2 (14,M)	PSGN	141/92	7.0	40.2	28.8	—	49.4
AGN3 (8,F)	PSGN	120/85	0.9	50.0	11.3	0.369	21.3
AGN4 (13,M)	PSGN	151/112	3.3	38.9	27.9	0.247	32.7
AGN5 (19,F)	PSGN	160/103	2.4	80.1	17.5	0.294	18.0
AGN6 (12,F)	—	136/90	5.4	36.2	21.9	0.067	52.3
AGN7 (13,M)	PSGN	128/91	4.1	61.2	7.9	0.064	40.4
AGN8 (12,M)	—	158/100	4.1	63.1	14.8	—	27.6
AGN9 (3,M)	PSGN	140/100	1.1	43.2	8.7	—	10.9
AGN10 (14,F)	PSGN	150/110	5.0	30.1	4.7	0.006	54.6
AGN11 (13,M)	—	140/100	1.1	28.1	17.5	0.178	24.8
AGN12 (2,F)	PSGN	130/80	—	72.1	17.6	0.075	39.5
AGN13 (6,M)	PSGN	120/85	—	55.5	10.8	—	10.2
AGN14 (5,M)	PSGN	137/83	0.8	80.1	9.3	0.572	4.86
AGN15 (5,M)	PSGN	160/110	1.3	52.1	12.6	0.178	8.07
AGN16 (4,F)	PSGN	143/88	1.7	88.1	26.5	0.108	15.8
Mean			2.84	55.0	16.16	0.187	27.2
± SEM			± 0.532	± 4.63	± 1.864	± 0.047	± 4.06
NS1 (18,M)	MPGN	160/112	3.0	40.2	26.5	0.506	12.5
NS2 (14,M)	MGN	130/100	3.5	80.1	6.0	1.342	5.4
NS3 (12,M)	MPGN	150/103	1.8	63.1	7.1	0.222	7.1
NS4 (8,F)	MCD[a]	90/79	3.1	108.9	15.6	0.778	6.8
NS5 (12,M)	MCD	130/80	4.8	131.1	18.5	—	4.1
NS6 (15,M)	PSGN	135/90	3.2	38.1	22.3	2.060	3.8
NS7 (12,M)	MGN (SLE)	118/75	2.5	68.6	22.5	1.811	2.1
NS8 (9,F)	MCD[a]	110/70	2.0	103.0	27.6	1.364	4.0
NS9 (11,M)	MCD[a]	90/65	6.3	98.3	13.3	1.072	3.8
Mean			3.36	77.9[c]	17.71	1.144[b]	5.5[b]
± SEM			± 0.47	± 11.55	± 2.618	± 0.222	± 1.02

Abbreviations are: AGN, acute glomerulonephritis (acute nephritic syndrome); NS, nephrotic syndrome with serum albumin <2.5 g/dl; PSGN, post-streptococcal glomerulonephritis; MPGN, membranoproliferative glomerulonephritis; MGN, membranous nephropathy; MCD, minimal change disease; SLE, systemic lupus crythematosus; PRA, plasma renin activity; ANF, atrial natriuretic factor; C_{Cr}, creatinine clearance corrected for 1.73 m^2.

[a] Biopsy not done. Edema calculated by the difference in admission weight and dry weigh after recovery (AGN) or remission (NS).

[b] $P < 0.001$ vs. patients with AGN

[c] $P < 0.001$ vs. patients with AGN

Table 2. Atrial natriuretic factor and renin activity in acute glomerulonephritis, nephrotic syndrome and controls

	$U_{Na}V$ *mEq/hr*	Weight gain *kg*	U protein g/day *range*	P albumin g/dl *range*	PRA *ng/liter · sec*	ANF *fmol/ml*
Controls (N = 18)						
20 mEq Na/day	0.93 ± 0.08	−0.050 ± 0.087	—	—	2.430 ± 0.190	3.450 ± 0.370
120–150 mEq Na/day	5.29 ± 0.18	0.001 ± 0.087	Neg	3.8–5.1	1.420 ± 0.143	6.220 ± 0.510
300 mEq Na/day	12.04 ± 0.44	0.892 ± 0.090	—	—	0.580 ± 0.060	11.560 ± 1.142
AGN (N = 16)	0.97 ± 0.11	2.840 ± 0.532	0.4–1.1	3.1–4.8	0.187 ± 0.047[a]	27.20 ± 4.06[a]
NS (N = 9)	1.06 ± 0.16	3.36 ± 0.47	4.1–7.2	1.8–2.4	1.144 ± 0.222[b]	5.51 ± 1.02[c]

Data in controls were obtained after 5 to 6 days in the corresponding Na diet. Urinary Na excretion ($U_{Na}V$) in controls was measured in 24-hour urine collections. Values of urinary Na excretion in AGN and NS patients were calculated from 4-hour urine samples obtained on admission. Abbreviations are: AGN, acute glomerulonephritis; NS, nephrotic syndrome; PRA, plasma renin activity; ANF, atrial natriuretic factor. Values are mean ± SEM, except for urinary protein excretion (U protein) and plasma albumin (P albumin) where the range is given.

[a] $P < 0.001$ vs. controls in any Na intake

[b] $P < 0.01$ vs. controls in high and low Na diets

[c] $P < 0.05$ vs. controls in low Na diet and $P < 0.01$ vs. controls in high Na diet

taken in convalescence) in patients 2, 6, 7, 10 and 15. Patients 1, 3, 5 and 14 did not have chest films repeated after recovery.

Cardiac output was determined on admission by echocardiography in five patients with AGN and one patient with NS. Three AGN patients showed increased cardiac output (N = 2.7 to 3.9 liter/min/m^2 surface area) and stroke index (N = 35 to 45

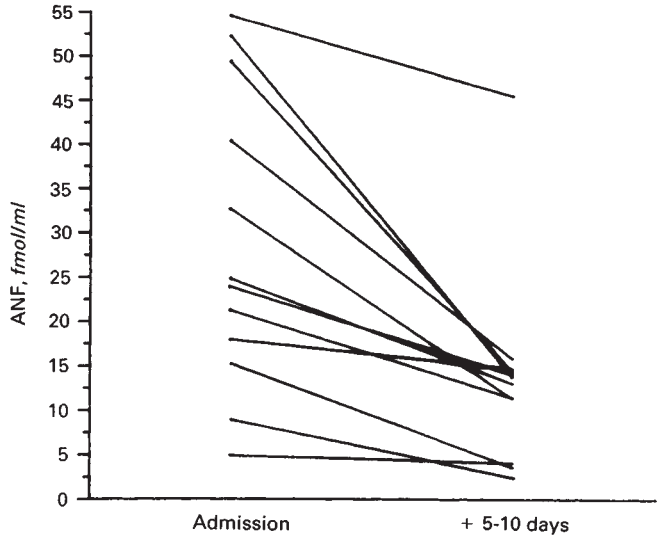

Fig. 1. *Individual values of plasma atrial natriuretic factor (ANF) in patients with acute glomerulonephritis.* Data correspond to values on admission and at the time when clinical edema had completely, or almost completely, resolved 5 to 10 days later. Only 12 patients are shown because the postacute data was not available in 4 of 16 patients.

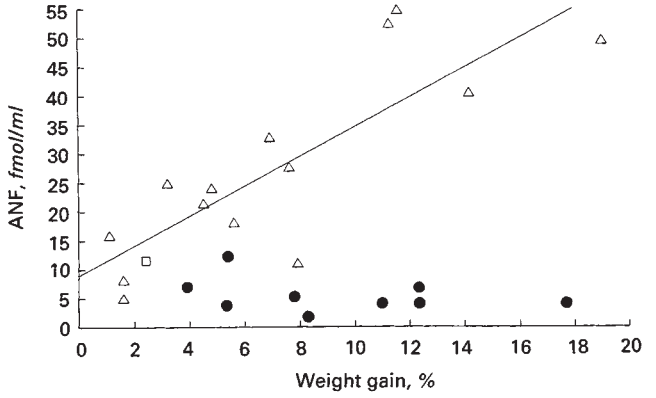

Fig. 2. *Relationship between plasma atrial natriuretic factor (ANF) and weight gain (calculated as the difference between admission weight and dry weight) expressed as percent change of dry weight.* The correlation in patients with acute glomerulonephritis (△) is highly significant ($r = 0.825$, $P < 0.001$, $Y = 9.37 + 2.55X$) but is not present in patients with nephrotic syndrome (●). Control subjects on a diet of 300 mEq Na per day are shown as the open square (mean ± SEM).

ml/min/m^2 surface area). Patient AGN2 (Table 1) had a cardiac output and stroke volume of 4.22 liter/min/m^2 and 49.7 ml/min/m^2, respectively; patient AGN8 had 4.53 liter/min/m^2 of cardiac output and 53.9 ml/min/m^2 stroke volume, and patient AGN10 had 7.77 liter/min/m^2 and 75.4 ml/min/m^2 of cardiac output and stroke index, respectively. Cardiac output was normal in patients AGN3 (3.10 liter/min/m^2) and in patient NS9 (3.5 liter/min/m^2). As shown in Table 1, this last patient had 6.3 kg of edema, corresponding to 17.7% increase in body weight.

Table 2 shows the data of control subjects in low, normal and high salt intake, in comparison with the mean data obtained in the patients. In controls in a low (20 mEq Na/day), regular (120 to 150 mEq Na/day) and high (300 mEq Na/day) salt intake, the urinary Na excretion in 24-hour urine collections were 22.3 ± 1.4 mEq Na/day, 126.9 mEq Na/day and 289.0 ± 10.35 mEq Na/day, (mean ± SEM) respectively. These data are shown as hourly Na excretion rates in Table 2 to compare it with the patients' data, which was obtained in one to four hour urine samples obtained on admission. Patients with AGN had ANF levels that were higher than the values observed in normal subjects on any sodium intake, including 300 mEq per day; correspondingly, PRA levels were more suppressed in AGN patients than in normals on a high salt diet. In contrast, the patients with NS had mean ANF and PRA levels that were comparable to those of normal individuals on a regular sodium diet (120 to 150 mEq Na per day). ANF levels were less stimulated in edematous nephrotic patients than in normal subjects on a high salt intake, and less suppressed than in sodium-retaining normal subjects (Table 2).

The acute nephritic syndrome of the patients with AGN had subsided, or was much improved, 5 to 10 days after admission; ANF levels decreased from 27.5 ± SEM 4.04 fmol/ml on admission, to 13.6 ± 3.19 fmol/ml at 5 to 10 days later. The individual patients are shown in Figure 1. ANF levels were determined in eight patients 4 to 12 weeks after discharge while on a free Na diet (not shown). At that time, ANF levels were 5.50 ± 0.80 fmol/ml, not significantly different from controls (6.22 ± 0.510 fmol/ml, Table 2).

Re-evaluation of ANF levels in remission and receiving no medication was only possible in four patients with the NS (patients NS4, NS5, NS6 and NS9). The changes observed after improvement in the nephrotic syndrome were inconsistent: patient NS6 had an increase in ANF levels in remission to 4.6 fmol/ml from the admission level of 3.8 fmol/ml. In contrast, patients NS4, NS5, and NS9 had a fall in their ANF levels (fmol/ml) to values of 3.6 (from 6.8 fmol/ml), 3.8 (from 4.1 fmol/ml) and 3.0 (from 3.8 fmol/ml), respectively.

There was a significant correlation between fluid retention and ANF stimulation in AGN. This was found whether fluid retention was expressed as absolute weight gain ($r = 0.888$, $P < 0.001$) or as percent increase above the dry weight ($r = 0.825$, $P < 0.001$). Figure 2 shows the later relationship in contrast with the lack of correlation between edema and ANF levels in the nephrotic syndrome.

Blood pressure was not correlated with ANF levels in AGN, but a significant correlation existed between mean arterial pressure (MAP) and ANF levels in NS patients ($r = 0.681$, $P < 0.05$).

Data obtained in all patients showed an exponential correlation between PRA and ANF levels ($r = -0.773$, $P < 0.0001$). Control subjects with various salt intakes fit well in the data of the AGN and NS patients (Fig. 3).

Discussion

The pathophysiology of edema in acute inflammatory renal disease is a subject of continued interest. Traditional explanations for sodium retention postulate that in the acute nephritic syndrome due to AGN, impaired sodium excretion is the result of an intrarenal disorder, while in the nephrotic syndrome the low urinary sodium is a compensatory response to a decreased "effective" intra-vascular volume.

In the case of AGN, several investigators [12, 13], including

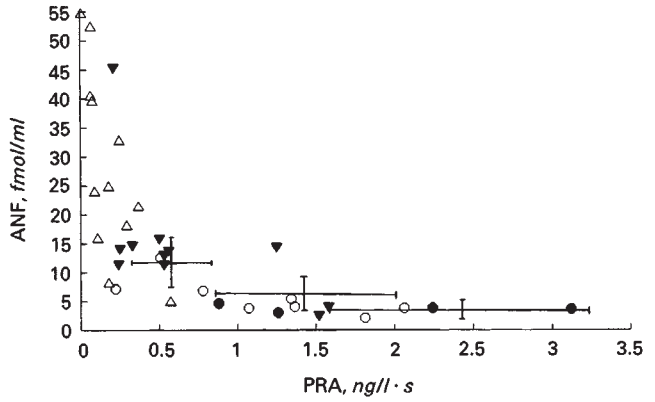

Fig. 3. *Exponential relationship [Y = exp(3.092 − 0.968X); r = −0.773, P < 0.0001] between atrial natriuretic factor (ANF) and plasma renin activity (PRA) in acute glomerulonephritis (open triangles, △, acute phase; closed triangles, ▼, convalescence), nephrotic syndrome (open circles, ○, crisis; closed circles, ●, remission) and controls (bars, mean ± SD) with intake of 20, 120 and 300 mEq Na per day.*

ourselves [11], have shown that PRA is appropriately suppressed in relation to the degree of fluid retention. To our knowledge, ANF levels previously have not been measured in patients with AGN, and the findings that we report in this paper are indicative of compensatory stimulation of ANF in response to sodium and fluid retention resulting from a primary intrarenal mechanism. Nevertheless, alterations in metabolism or clearance of ANF in AGN may play a contributing role in patients with severely impaired renal function. The increased cardiovascular overload of patients with AGN was evident in the clinical findings at their admission. Cardiac output was increased in three AGN patients and normal in another two. The existence of high-output heart failure in many patients with AGN is a well-recognized finding [reviewed in ref 14], unfortunately, a critical assessment of atrial size was not made and correlations with this parameter are not possible. However, the fall of ANF values after diuresis was begun and edema had resolved (Fig. 1), and the further decrease of ANF after 4 to 12 weeks of convalescence to levels similar to control subjects in convalescence, are congruent with a compensatory hormonal stimulation. The striking correlation between the degree of fluid retention (estimated by the difference in weight between admission and recovery) and the levels of ANF, shown in Figure 2, is also consistent with this interpretation. It is also possible that the half-life of ANF was prolonged in the patients with markedly depressed GFR. This factor, per se, appears to be less important than volume expansion since ANF levels are not correlated with creatinine clearance. However, it could certainly have contributed to the high ANF values found in patients AGN2, AGN6 and AGN10, who had creatinine clearances (which in renal failure overestimate GFR) of 30 to 40 ml/min/1.73 m^2 (Table 1). Renal function was more impaired in patients with AGN than in patient with NS (Table 1), but this cannot explain the differences between NS and AGN since patients NS1 and NS6 had creatinine clearances which were depressed to a similar degree as patients AGN2, AGN6 and AGN10, yet had much lower ANF levels.

The situation in patients with NS is more complex. Plasma volume has been found to be decreased in only 30% of the patients with NS, while the rest have normal or increased values [3]. Determinations of plasma volume depend on the distribution of the marker and overestimation is expected if there is leaking out of the vascular tree. Even if the error introduced in this fashion is small, as suggested by Geers et al [15], measurements of plasma volume are suspect in hypoalbuminemic patients. Because of these difficulties, attention has been turned to the volume sensitive hormones that may reflect the "effective" or perceived state of intravascular filling. Yet, the role of volume sensitive hormones in the sodium retention remains a matter of controversy. Patients with full blown nephrotic syndrome have low urinary sodium excretion and edema, as do patients with AGN, but they also have hypoalbuminemia. Alteration of Starling's equilibrium forces resulting from decreased oncotic pressure facilitates fluid movement out of the vascular system. Therefore, hypoalbuminemia should exert a dampering effect on the stimulation of volume-sensing mechanisms in a fluid retaining patient. In these circumstances, a better insight is gained if the hormonal responses are compared in groups of patients with comparable edema and urinary sodium excretion, who present (nephrotics) or not (acute glomerulonephritis) with hypoalbuminemia. In addition, appropriateness of a response may be best evaluated in comparison with controls with physiologically stimulated (low sodium diet) or maximally suppressed (high sodium diet) urinary sodium excretion (Table 2).

The levels of ANF in normal subjects on 120 to 150 mEq Na per day (6.22 ± 0.51 fmol/ml, SE, Table 2) are comparable to findings from our laboratories reported previously in the general population (5.77 ± 0.37 fmol/ml, SEM, $N = 45$) [8]. Changes in sodium intake induced variation in PRA and ANF levels in our control subjects which are comparable to those reported by others [11, 16, 17]. It is interesting that patients with NS resemble, with respect to their ANF and PRA levels, normal individuals on a regular sodium intake who are neither intensely retaining or eliminating sodium (Table 2). The results are not different from the findings in several reports which show that nephrotic patients as a group have mean levels of PRA [1–5] and ANF [6, 7] within the limits found in normals in unrestricted sodium intake. In fact, some of the confusion pertaining to levels of volume sensitive hormones in NS may be due to defining "low" or "high" levels in relation to normals, whose sodium intake may vary widely, and to the lack of control determinations in normals during hormonal suppression and stimulation.

There is no correlation between edema and ANF levels in NS patients (Fig. 2). Only the three values of ANF in nephrotics (NS1, NS3, NS4), are within 2 SD of the mean value of ANF in normals stimulated with a high salt diet (11.56 ± 4.84 fmol/ml, SD). Therefore, it is evident that ANF and PRA responses do not promote maximal sodium excretion in nephrotic patients, though fluid retention ranged from 1.8 kg to 6.3 kg (Table 1), representing 6% and 22% gain in body weight, respectively. By similar reasoning, ANF and PRA responses in NS also do not actively retain sodium, since the levels of these hormones do not meet the values found in normals on a low sodium diet (Table 2).

Evaluation of PRA and ANF in a spectrum of patients and controls permitted a wide range of physiologic and pathophysiologic levels of these hormonal systems to be covered which

have opposing actions on sodium and water balance; an exponential relationship with a strong negative correlation was found (Fig. 3). From this relationship it may be appreciated that in volume-contracted sodium retaining states, changes in the stimulated PRA levels are more sensitive than changes in the correspondingly suppressed ANF levels; the opposite is true in conditions characterized by volume expansion. As shown in Figure 3, patients with AGN and normal individuals on a sodium restricted diet occupy the opposite ends of the hormonal volume-sensing reponse. Patients with NS are located in the middle ground alongside controls on a regular sodium diet.

Our findings suggest that volume sensitive hormones are not responsible for the fluid and sodium retention in patients with NS. Work from other laboratories has also failed to incriminate extrarenal hormonal influences in the sodium retention of these patients: Brown et al [18] and Koomans et al [19] have reported that plasma expansion to normal levels failed to reverse the positive sodium balance, and Peterson et al [20] found that increments of plasma ANF induced with water immersion were not associated with a normal natriuretic response. Captopril-induced suppression of the renin-angiotensin system failed to produce a natriuresis [18]. Finally, experimental studies injecting puromycin aminonucleoside in one renal artery have shown that the affected nephrotic kidney, but not the contralateral control, retains sodium despite the absence of hypoalbuminuria and, therefore, with a presumably non-contracted intravascular volume [21, 22].

In view of the accumulated clinical and experimental evidence and our own data reported here, it appears likely that intrarenal mechanisms are responsible for fluid retention in both NS and AGN. The existence or absence of hypoalbuminemia may be one of the factors responsible for a different level of stimulation of the systems involved in volume homeostasis in the patients with AGN and NS. These systems are clearly sensing a more expanded intravascular status in patients with AGN at all levels of fluid retention than in patients with NS, and are responding accordingly (Fig. 2).

It is, of course, conceivable that the "suboptimal" ANF responses to fluid retention observed in the patients with NS, shown in Figure 2, could be the result of defects in the sensing volume receptors or in the production of ANF. However, these possibilities appear unlikely because ANF stimulation after head-out water immersion and volume expansion is normal or supranormal in these patients [7, 20].

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References

1. Medina A, Davies DL, Brown JJ, Fraser R, Lever AF, Mallick NP, Morton JJ, Robertson JIS, Tree M: A study of the renin-angiotensin system in the nephrotic syndrome. *Nephron* 12:233–240, 1974
2. Meltzer JI, Keim HJ, Laragh JH, Sealey JE, Jan KM, Chien S: Nephrotic syndrome: Vasoconstriction and hypervolemic types indicated by renin-sodium profiling. *Ann Intern Med* 91:688–696, 1979
3. Dorhout Mees EJ, Roos JC, Boer P, Yoe OH, Simatupang TA: Observations on edema formation in the nephrotic syndrome in adults with minimal lesions. *Am J Med* 67:378–384, 1979
4. Boer P, Roos IC, Geyskes GG, Dorhout Mees EJ: Observations on plasma renin substrate in the nephrotic syndrome. *Nephron* 26:121–125, 1980
5. Brown EA, Markandu ND, Roulston JE, Jones BE, Squires M, MacGregor GA: Is the renin-angiotensin-aldosterone system involved in the sodium retention in the nephrotic syndrome? *Nephron* 32:102–107, 1982
6. Rabelink AJ, Koomans HA, Gaillard CA, Dorhout Mees EJ: Renal response to atrial natriuretic peptide in nehrotic syndrome. *Nephrol Dial Transplant* 2:510–514, 1987
7. Tulassay T, Rascher W, Lang RE, Seyberth HW, Sharer K: Atrial natriuretic peptide and other vasoactive hormones in nephrotic syndrome. *Kidney Int* 31:1391–1393, 1987
8. Rodríguez-Iturbe B, Herrera J, Gutkowska J, Parra G, Coello J: Atrial natriuretic factor increases after a protein meal in man. *Clin Sci* 75:495–498, 1988
9. Gutkowska J, Bourassa M, Roy D, Thibault G, Garcia R, Genest J, Cantin M: Immunoreactive atrial natriuretic factor (IR-ANF) in human plasma. *Biochem Biophys Res Com* 128:1350–1357, 1985
10. Gutkowska J, Bonan R, Roy D, Bourassa M, Garcia R, Thibault G, Genest J, Cantin M: Atrial natriuretic factor in human plasma. *Biochem Biophys Res Com* 139:287–295, 1986
11. Rodríguez-Iturbe B, Baggio B, Colina-Chouria J, Favaro S, Garcia R, Sussana F, Castillo L, Borsatti A: Studies on the renin-aldosterone system in the acute nephritic syndrome. *Kidney Int* 19:445–453, 1981
12. Birkenhager WH, Schalekamp MAD, Schalekamp-Kuyen MAP, Kolsters G, Drauss XH: Interrelations between arterial pressure fluid volume and plasma-renin concentration in the course of acute glomerulonephritis. *Lancet* 1:1086–1087, 1970
13. Powell HT, Rotenberg E, Williams AL, McCredie DA: Plasma renin-activity in acute poststreptococcal glomerulonephritis and haemolytic-uremic syndrome. *Arch Dis Child* 49:802–807, 1974
14. Rodríguez-Iturbe B, Parra G: Loop diuretics and angiotensin converting enzyme inhibitors in the acute nephritic syndrome, in *Diuretics II, Chemistry, Pharmacology and Clinical Applications*, edited by JB Puschett, A Greenberg, New York, Elsevier Publishers, 1987, pp. 536–540
15. Geers AB, Koomans HA, Boer P, Dorhout Mees EJ: Plasma and blood volumes in the nephrotic syndrome. *Nephron* 38:170–174, 1984
16. Pratt H, Luft F: The effect of extremely high sodium intake on plasma renin activity, plasma aldosterone concentration and urinary excretion of aldosterone metabolites. *J Lab Clin Med* 93:724–729, 1979
17. Brown JJ, Davies DL, Lever AF, Robertson JIS: Influence of sodium loading and sodium depletion on plasma-renin in man. *Lancet* 2:278–279, 1963
18. Brown EA, Markandu ND, Sagnella GA, Squires M, Jones BE, MacGregor GA: Evidence that some mechanisms other than the renin system causes sodium retention in the nephrotic syndrome. *Lancet* 2:1237–1239, 1982
19. Koomans HA, Geers AB, Meiracker AH, Roos JC, Boer P, Dorhout Mees EJ: Effect of plasma volume expansion on renal salt handling in patients with nephrotic syndrome. *Am J Nephrol* 4:227–234, 1984
20. Peterson C, Madsen B, Perlman A, Chan AYM, Myers BD: Atrial natriuretic peptide and the renal response to hypervolemia in nephrotic humans. *Kidney Int* 34:825–831, 1988
21. Chandra M, Hoyer JR, Lewy JE: Renal function in rats with unilateral proteinuria produced by renal perfusion with aminonucleoside. *Pediatr Res* 15:340–344, 1981
22. Ichikawa I, Rennke HG, Hoyer JR, Badr KF, Schor N, Troy JL, Leehene CP, Brenner BM: Role for intrarenal mechanisms in impaired salt excretion of experimental nephrotic syndrome. *J Clin Invest* 71:91–103, 1987