Dear Sir,

Endothelin is a potent vasoconstrictor peptide isolated from the culture medium of vascular endothelial cells (1). Recent studies show that endothelin decreases sodium excretion directly or indirectly by changes in renal hemodynamics [2-3]. If endothelin plays a role in the sodium and water homeostasis, then its production and secretion may be altered in various pathologic states associated with hyponatremia. To prove this hypothesis, we measured plasma levels of endothelin-1, the major molecular form of endothelin peptides present in human plasma [4], in patients with hyponatremia of different causes.

We studied 6 men with the syndrome of inappropriate antidiuretic hormone secretion (SIADH), aged 53-72 years. The diagnosis was established by the criteria of Schwartz et al. [5]. All patients had hyponatremia (mean ± SD: 119 ± 6 mmol/l) and plasma hypoosmolality (241 ± 11 mmol/kg), despite hypertonic urine (431 ± 5 mmol/kg) and sustained urinary sodium excretion (102 ± 28 mmol/l). Their underlying diseases were head injuries in 3, lung cancer in 2, and gastric cancer in 1 patient. We studied also 6 men (aged 64-73 years) with depletional hyponatremia, which resulted from excessive use of diuretics or mannitol infusion in 3 patients with isolated ACTH deficiency, in 2 with head injuries and in 1 with liver cirrhosis. They had hyponatremia (mean ± SD: 121 ± 6 mmol/l) and plasma hypoosmolality (249 ± 18 mmol/kg) and excreted hypertonic urine (564 ± 198 mmol/kg) with urinary sodium loss (107 ± 90 mmol/l). The patients were dehydrated and their plasma creatinine

\[ p < 0.01 \]

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<th>Patients</th>
<th>Normal with SIADH</th>
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<td>Patients</td>
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Fig. 1. Plasma endothelin-1 levels in patients with SIADH, in patients with depletional hyponatremia and in age-matched normal men. Bars represent mean ± SD.

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levels and plasma renin activity were elevated. Plasma endothelin-1 levels were measured by
sandwich-type enzyme immuno-assay with the use of reagents provided by Takeda Chemical
Industries, Osaka, Japan, as previously reported [4].

Figure 1 shows plasma endothelin-1 levels in these two groups of patients and in 6 age-
matched normal men. The mean (± SD)

plasma endothelin concentration in patients with SIADH (0.5 ± 0.2 pmol/l) was significantly
(p < 0.01) lower than in normal subjects (0.9 ± 0.1 pmol/l) which could not be explained
simply by hemodilution associated with SIADH. When hyponatremia was corrected by fluid
restriction or demeclocycline administration, plasma endothelin-1 levels rose to normal. In
contrast, the mean (± SD) plasma endothelin-1 concentration in patients with depletional
hyponatremia (1.1 ± 0.2 pmol/l) was significantly (p < 0.01) higher than in controls, although
the mean plasma sodium concentration and osmolality in this group of patients were not
statistically different from those in patients with SIADH, suggesting that the difference in
plasma endothelin-1 levels in the two groups was occasioned by a different plasma volume
status rather than low plasma sodium or osmolality.

Again, correction of hyponatremia with supplementation of salt and fluid lowered plasma
endothelin-1 levels to normal.

A variety of humoral and neutral mechanisms may operate in hyponatremia to normalize the
sodium and water balance. The above findings indicate that endothelin may be one of such
factors. In hyponatremia with plasma volume depletion, the production and secretion of
endothelin by vascular endothelial cells may be increased, thus decreasing further renal
sodium loss [2-3] on one hand, and causing vasoconstriction to prevent a fall in blood
pressure [1] on the other. The opposite may occur in hyponatremia with volume excess such
as SIADH. The mechanism responsible for altered production and secretion of endothelin in a
different plasma volume status should be clarified by future studies.

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