Prevention with Thiazide of NaCl-Induced Hypertension in Dahl "S" Rats
Evidence for a Na-Retaining Humoral Agent in "S" Rats

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SUMMARY Dahl “S” rats become hypertensive when fed a high salt (NaCl) diet but remain normotensive on a low NaCl diet. Dahl “R” rats are normotensive on either diet. For a given perfusion pressure, isolated “S” kidneys excrete 50% less sodium than “R” kidneys. Therefore, we searched for a sodium-retaining hormone in “S” rats. Kidneys were isolated without ischemia from normal rats and were continuously perfused at 125 mm Hg with blood from Dahl “S” and “R” rats, all on low NaCl diets. All kidney and adrenal tissue had been extirpated from the perfusing rats. During 15 minutes of perfusion, the isolated “normal” kidneys excreted a mean of 164 μEq Na/min/100 g during 26 perfusion experiments with blood from “R” rats. The “normal” kidneys excreted a mean of 84 μEq Na during 24 perfusions with blood from “S” rats. Thus, the normal kidneys excreted half as much sodium when perfused with “S” blood compared with “R” blood (p < 0.02). Seemingly, a Na-retaining humoral agent is present in the blood of “S” rats on a low Na diet, in the absence of renal and adrenal tissue. Moreover, in these normal kidneys, perfusion with “S” blood induced a 16% higher renal vascular resistance than perfusion with “R” blood (p < 0.01), indicating vasoconstricting agents in “S” blood. However, the Na-retaining humoral effect is definitely not dependent on the vasoconstriction. The Na-retaining humoral effect in “S” blood could lead to Na retention by “S” kidneys in vivo, which could partially account for the susceptibility of “S” rats to NaCl hypertension. Furthermore, both “S” and “R” perfusing rats were continuously expanded with two-thirds blood and one-third Ringer’s solution at a rate of 5% of body weight per hour. This expansion induced the appearance of a natriuretic humoral agent in the blood of both “S” and “R” rats to an equal degree, so that after 45 minutes of expansion, the isolated kidneys had increased their Na excretion approximately twofold. Hypertension is readily induced in Dahl “S” rats by feeding them a high NaCl diet. However, this hypertension can be almost completely prevented by concomitant treatment with thiazide diuretics that act mainly on the kidney to facilitate sodium excretion. This result is in agreement with the hypothesis that a shift in the pressure natriuresis curve, reducing Na excretion for a given arterial pressure, is partially responsible for the great sensitivity to NaCl hypertension in the “S” rat. The Na-retaining hormone may contribute to this shift. (Hypertension 1: 316-323, 1979)

KEY WORDS • NaCl hypertension • genetic hypertension • thiazide diuretics • sodium excretion • anti-natriuretic humoral agents • natriuretic humoral agents

JUDGING from numerous studies in primitive human societies,1-8 it is apparent that human subjects susceptible to essential hypertension will become hypertensive if they eat 150 to 200 mEq of salt daily, but will fail to become hypertensive if they are on a lifelong low sodium intake of less than 50 mEq daily. Thus, their hypertension is related to and governed by the intake of NaCl. On the other hand, human subjects resistant to hypertension can easily eat 200 mEq of sodium daily without showing any rise in blood pressure at all. One could theorize that certain people are susceptible to hypertension because of a basic difficulty in accomplishing the rapid excretion of a Na load. If such a person is on a lifelong low intake of Na, there would be no tendency for accumulation of Na in the body, in spite of the defect in Na excretion, and, therefore, no stimulus for a rise in blood pressure. However, with a high intake of Na, such a limitation of natriuresis would bring about an initial accumulation of body Na that would trigger a rise in blood pressure. This rise in pressure would then, through pressure natriuresis, correct the sluggish Na excretion.
This proposition cannot easily be tested in hypertensive and normotensive humans, because hypertensive man has a higher pressure in the renal artery, which is a well-known stimulus for accelerating natriuresis. However, the proposition could be tested in the two strains of Dahl rats, because both strains have normal blood pressures on a low sodium diet. With a high sodium diet, the “S” strain becomes severely hypertensive, while the “R” strain has no rise in pressure at all. In this experiment, isolated kidneys were obtained from normotensive “S” and “R” rats on a low sodium diet and were mounted in a chamber without ischemia and perfused with blood from normal rats at varying perfusion pressures. The pressure natriuresis curve for kidneys from “S” rats was definitely shifted to the right, such that it took a greater level of inflow pressure to bring about a given rate of natriuresis (fig. 1). When compared at inflow pressures of 100, 130 and 160 mm Hg, the “S” kidneys excreted half as much Na/min as the “R” kidneys. Moreover, the slower natriuresis of the “S” kidney could be easily overcome by raising the perfusion pressure. Thus, an “S” kidney perfused at 160 mm Hg excreted about 50% more Na than a normotensive “R” kidney perfused at a normal 130 mm Hg. This study indicated that the kidney of prehypertensive “S” rats did indeed have a reduced rate of natriuresis and seemed to require comparatively higher perfusion pressures for any given rate of Na excretion, even though these kidneys had no visible pathological lesions whatsoever. Such a shift in the pressure-natriuresis curve, if present in vivo, could lead to a NaCl-induced hypertension. If this were true in vivo for the Dahl “S” rat, then diuretic drugs, which facilitate Na excretion, should be able to prevent the NaCl-induced hypertension. This proposition was tested in the following experiments.

Methods

Experiment 1

Twelve “S” rats and 15 “R” rats were treated for 14 weeks after weaning with a thiazide diuretic, by adding 0.1 g of methyclothiazide to each liter of drinking water. This dose was selected since previous studies had indicated that it provided a near maximum diuretic effect when given over a 3-day period. Fourteen “S” and 13 “R” rats did not receive the thiazide diuretic in their drinking water and served as controls. All rats were maintained on a diet containing 0.3% NaCl during this 14-week treatment period. Drinking was ad libitum. Then, all four groups of rats were abruptly switched to an 8% NaCl diet, as the diuretic regimen continued uninterrupted (fig. 2). The blood pressure of each rat was determined at weekly intervals during the entire experiment, by means of the microphonic method of Friedman and Freed without anesthesia.
Experiment 2

It still remains uncertain as to why the "S" kidney requires a higher pressure for a given rate of sodium excretion (fig. 1). Some type of sodium-retaining hormone in "S" rats is one possible explanation. To investigate this possibility, we connected a "normal" isolated Sprague-Dawley kidney to the circulation of either a Dahl "S" rat or a Dahl "R" rat and observed the ensuing excretion of Na by the isolated kidney, which was being perfused at a fixed inflow pressure. The isolated kidney thus serves as a bioassay organ to detect natriuretic or antinatriuretic humoral agents. We obtained the isolated kidneys from normal Sprague-Dawley rats without any period of ischemia whatsoever. This was done by cannulating the aorta and vena cava below the renal arteries and starting the perfusion of the kidney from below. Then, the aorta and vena cava are clamped off above the renal arteries, as perfusion continues uninterrupted from below the kidney. The isolated kidneys were placed in a warm chamber (37°C) after they were connected to the circulation of either a normotensive "S" rat or a normotensive "R" rat and were perfused with heparinized arterial blood (fig. 3). By raising or lowering the perfusing rat, the inflow pressure to the isolated normal kidney could be held at 125 mm Hg. Venous blood was then pumped back from the isolated kidney to the perfusing rat. Since we were searching for some anti-natriuretic hormonal effect not involving the renin-aldosterone system, we extirpated all kidney and adrenal tissue from the perfusing rat 60 minutes before perfusion to remove any endogenous source of renal or adrenal hormones. Aldosterone (10 ng/min per rat) and cortisol (30 μg/min) were given intravenously during this time for replacement. After a priming dose, 14C-inulin was given in the same infusion solution (0.0065 μCi/min). Moreover, the isolated kidney was exposed for 10 minutes to phenoxybenzamine before it was connected to the perfusing rat, in order to block α-adrenergic effects upon it, up to a dose of 5 μg of norepinephrine into the renal artery. The first 7 ml of blood that flowed from the perfusing rat through the isolated kidney were discarded, in order to flush any excess unfixed phenoxybenzamine out of the isolated kidney, thus making certain that the perfusing rat was not exposed to the phenoxybenzamine. Extra blood from another rat was added to the venous reservoir to replace the discarded blood. Both "S" and "R" rats had been eating the 0.3% NaCl diet before entering the perfusion experiment.

The isolated kidney was perfused for 20 minutes to allow for equilibration of the system. Then a 15-minute urine collection was begun. After this 15-minute period of urine collection had been completed, we expanded the perfusing rat with a mixture of two-thirds rat blood and one-third Krebs' solution, infused over a 1-hour period at a rate of 5% of the body weight per hour. This is divided in such a way that 1.55% of the body weight is infused steadily during the first 15 minutes of infusion, while 3.45% of the body weight is infused steadily during the last 45 minutes of infusion. This schedule allows for a slightly faster rate of expan-
sion during the first 15 minutes. Urine was collected in four 15-minute samples during the 1-hour expansion. This method of expansion was selected since earlier studies had indicated that it would stimulate the appearance of natriuretic hormonal agents in the blood of the perfusing rat. It also allows an expansion with virtually no change in hematocrit or colloid osmotic pressure. We wondered whether or not the "S" and the "R" rats would be able to produce these natriuretic hormonal agents. Renal blood flow was ascertained for each urine-collection period by direct counting of drops, combined with an accurate estimation of the volume of the drops. Glomerular filtration rate (GFR) was estimated from inulin clearance during each urine-collection period. Since both pressure and flow were known, it was also possible to calculate renal vascular resistance. The colloid osmotic pressure of plasma was directly measured with an IPM microosmometer, with a PM-30 Amicon membrane. Hematocrit of the blood entering the isolated kidney was also measured.

Results

Experiment 1

As indicated in figure 2, the "R" rats, either on or off thiazide, had no rise in blood pressure while on the high salt diet. Blood pressure in this group averaged 135 mm Hg, after 9 weeks on the high salt diet. On the other hand, the "S" rats not protected by the thiazide diuretic immediately began a stepwise week-by-week increase in blood pressure when they began eating the 8% NaCl diet. Their average blood pressure had risen to 210 mm Hg by the 8th week of the high salt diet. In striking contrast to this, one notes that the "S" rats that were protected by the thiazide diuretic had virtually no rise in blood pressure when they began the high salt diet. Their blood pressure line moves parallel with that of the "R" rats and only about 5 mm Hg above it. After 9 weeks of the high salt diet, their blood pressures averaged 140 mm Hg. Thus, treatment with the thiazide diuretic almost completely prevented the NaCl hypertension in the "S" rat. Apparently, the action of the thiazide to facilitate Na excretion overcomes the reduced rate of Na excretion in "S" kidneys and thereby prevents the tendency for an initial accumulation of body sodium. Thus, there would be no Na stimulus for a rise in blood pressure, and pressure would remain at normal levels. Ordinary thiazide diuretics, including the methyclothiazide used here, do not have any direct action on arterioles and venules. Their action is mainly on the distal nephron to enhance Na excretion. The fact that they were effective in preventing NaCl-induced hypertension fits in with the hypothesis that a shift in the pressure-natriuresis curve in vivo is at least partially responsible for the great susceptibility to NaCl hypertension in the "S" rat. Moreover, since thiazide diuretics are such effective anti-hypertensive agents in man, one wonders whether some type of aberration of natriuresis might not also be present in the kidneys of those with essential hypertension.

This study was also designed to investigate another facet in the blood pressure of Dahl rats. Even though
the blood pressure of 12-week old "S" rats is within the normal range during the feeding of a low (0.3%) salt diet, it is still about 16 mm Hg higher than that of the "R" rats. In figure 2, as indicated by the black dots and triangles, one sees that the blood pressure of untreated "S" and "R" rats on a 0.3% NaCl diet is at the same level through 7 weeks after weaning. From then on, the average pressure of the "S" rats begins to climb above that of the "R" rats, until by 12 weeks of age the pressure of the "S" rats is 16 mm Hg above that of the "R" rats, a significant difference (p < 0.001). It has always been an intriguing question as to whether this 16-mm Hg difference in pressure was hypertension that was unrelated to NaCl balance, just as almost all of the hypertension of Kyoto Okamoto spontaneously hypertensive rats is unrelated to NaCl balance. The treatment with the thiazide diuretic gave some insight into this question. During the 14th week on the 0.3% NaCl diet, the "S" rats on thiazide had an average blood pressure only 5 mm Hg higher than that of the "R" rats. Thus, without thiazide, the blood pressure difference was 16 mm Hg. With thiazide treatment, the pressure difference is reduced to 5 mm Hg, a significant difference (p < 0.001). This would indicate that two-thirds of this small elevation of blood pressure in "S" rats can be eliminated by thiazide diuretics. Hence, two-thirds of this small elevation of pressure appears to be related to NaCl balance and is probably induced by the 0.3% NaCl in the diet. Actually, this level of NaCl in the diet is three times the minimum requirement for NaCl in the diet of adult rats. This leaves us with a statistically significant (p < 0.001) 5-mm Hg elevation of pressure in "S" rats on thiazide, which seems not to be related to NaCl balance after weaning.

### Experiment 2

As seen in table 1, in 26 experiments in which the normal kidney was perfused by blood from an "R" rat, the average sodium excretion was 164 μEq/min/100 g kidney. In 24 experiments in which the normal kidney was perfused by blood from a prehypertensive "S" rat, the sodium excretion averaged 84 μEq/min. Thus, when "S" blood is flowing through the isolated kidney, the rate of sodium excretion is reduced by half as much as when "R" blood is perfusing the isolated kidney (p < 0.02). Since the inflow pressure

### Table 1

<table>
<thead>
<tr>
<th>Perfusions of normal kidneys</th>
<th>Sodium excretion (μEq/min/100 g kidney)</th>
<th>Urine volume (μl/min/10 g kidney)</th>
<th>Renal blood flow (ml/min/10 g kidney)</th>
<th>Glomerular filtration rate (ml/min/10 g kidney)</th>
</tr>
</thead>
<tbody>
<tr>
<td>26 perfusions by &quot;R&quot; rate</td>
<td>164 ± 30</td>
<td>99 ± 14</td>
<td>39.2 ± 1.3</td>
<td>7.3 ± 0.3</td>
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<tr>
<td>24 perfusions by prehypertensive &quot;S&quot; rate</td>
<td>84 ± 16</td>
<td>62 ± 6</td>
<td>33.7 ± 1.6</td>
<td>6.2 ± 0.3</td>
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Reduction (%): -49 < 0.02

<table>
<thead>
<tr>
<th>Reduction (%)</th>
<th>p value</th>
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<tr>
<td>-37</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>-14</td>
<td>&lt;0.01</td>
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<tr>
<td>-15</td>
<td>&lt;0.05</td>
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* = indicates SEM.

### Table 2

<table>
<thead>
<tr>
<th>Kidney perfusions with matched renal resistance</th>
<th>Sodium excretion (μEq/min/100 g kidney)</th>
<th>GFR (ml/min/10 g kidney)</th>
<th>Fraction of filtered Na excreted (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>23 perfusions by &quot;R&quot; rate (34.8 renal resistance units)</td>
<td>173 ± 33</td>
<td>7.1 ± 0.3</td>
<td>1.8 ± 0.3</td>
</tr>
<tr>
<td>21 perfusions by prehypertensive &quot;S&quot; rate (35.1 renal resistance units)</td>
<td>75 ± 8</td>
<td>6.5 ± 0.3</td>
<td>0.9 ± 0.1</td>
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Reduction (%): -57

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<td>&lt;0.006</td>
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<tr>
<td>NS</td>
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<tr>
<td>&lt;0.01</td>
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</table>

*The perfusion experiments in this table were selected to provide an equal average renal vascular resistance in the two groups being compared. ± indicates SEM.
was held constant, this difference in the rate of natriuresis is most likely explained by humoral agents in the blood of these rats. Urine flow was also reduced by 37% in perfusions with “S” rats (p < 0.02).

Table 1 also shows the renal blood flow in the isolated kidneys perfused at a constant pressure. The average blood flows were 39.2 ml/min/10 g of kidney in 26 kidneys perfused with “R” blood versus 33.7 ml/min/10 g in 24 kidneys perfused with “S” blood. Thus, the average blood flow was reduced 14% in kidneys perfused with “S” blood (p < 0.01). Since perfusion pressure was the same in the two groups, this indicates that perfusion with “S” blood results in a 16% increase in renal vascular resistance. Presumably, humoral agents in “S” blood somehow cause a vasoconstriction in the isolated kidney. The glomerular filtration rate was also 15% lower in the kidneys perfused with “S” blood (p < 0.05). This percentage reduction is similar in magnitude to the reduction in renal blood flow. A predominantly afferent vasoconstriction could account for the similar degree of reduction in both blood flow and glomerular filtration.

It is well established that vasodilatation in a kidney usually heightens Na excretion, while vasoconstriction usually decreases it. Thus, it is quite logical to believe that the vasoconstriction in the kidneys supplied with blood from “S” rats would account, at least in part, for the 49% reduction of Na excretion in these same kidneys. To investigate this, we wanted to nullify the effect of increased vasoconstriction in the kidneys perfused with “S” blood. We did this by discarding the three perfusions by “R” rats with the lowest renal vascular resistances (table 2), the GFR in “S” perfusions was about 8.5% lower than in “R” perfusions, although this difference was not significant. Nevertheless, this difference in GFR could conceivably have a large effect on Na excretion. To nullify this effect, we discarded the four “R” perfusions with the highest GFR and discarded the four “S” perfusions with the lowest GFR. This left 22 “R” perfusions and 20 “S” perfusions, in which the GFR happened to average 6.77 ml/min/10 g kidney for each of the two groups. In these two groups, matched for GFR, the Na excretion was 152.0 μEq/min/100 g kidney for the 22 “R” perfusions and was 91.7 for the 20 “S” perfusions. Thus, even when the GFR was equal in the two groups, the rate of Na excretion in “S” perfusions was 40% slower than in “R” perfusions (p = 0.09).

When this difference in Na excretion became apparent, we decided to find out whether we had an antinatriuretic humoral effect in “S” rats or a pro-natriuretic humoral effect in “R” rats. To answer this question, we began a “round-robin” rotation of experiments which included regular normal Sprague-Dawley rats as the perfusing rats, along with the Dahl “S” and “R” rats. Table 3 gives the Na excretion for these three groups, which averaged 161 μEq/min/100 g kidney for the “R” rats, compared to 76 for the “S” rats and 150 for the Sprague-Dawley rats. The excretion for the “S” rats was 53% lower than that of the

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<th>Sodium excretion (μEq/min/100 g kidney)</th>
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<th>Glomerular filtration rate (ml/min/10 g kidney)</th>
<th>Fraction of filtered Na excreted (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 perfusions by “R” rats</td>
<td>161 ± 37</td>
<td>118 ± 7</td>
<td>10.2 ± 0.9</td>
<td>1.23 ± 0.3</td>
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<td></td>
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<td>0.06</td>
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<tr>
<td>8 perfusions by prehypertensive “S” rats</td>
<td>76 ± 16</td>
<td>77 ± 8</td>
<td>7.7 ± 1.0</td>
<td>0.65 ± 0.1</td>
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<td>NS</td>
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<td></td>
<td>NS</td>
</tr>
<tr>
<td>8 perfusions by Sprague-Dawley rats</td>
<td>150 ± 36</td>
<td>113 ± 13</td>
<td>9.3 ± 0.7</td>
<td>1.39 ± 0.4</td>
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*This series was carried out in “round-robin” fashion to compare Sprague-Dawley rats with the two strains of Dahl rats. = indicates SEM.
"R" rats ($p < 0.05$) and was 50% lower than that of the Sprague-Dawley rats ($p < 0.07$). The urine flow rate averaged 118 μl/min/10 g kidney for "R" perfusions compared with 77 for "S" perfusions and 113 for Sprague-Dawley perfusions. The urine flow rate for the "S" rats was 35% lower than that of the "R" rats ($p < 0.001$) and was 32% lower than that of the Sprague-Dawley rats ($p < 0.03$). The fractional Na excretion of the "S" rats was 47% lower than that of the "R" rats ($p < 0.06$). The fractional Na excretion of the Sprague-Dawley rats closely resembled that of the "R" rats, but was more than twice as great as that of the "S" rats. Overall, it appeared that the Sprague-Dawley rats closely resembled the "R" rats and were quite different from the "S" rats with regard to humoral agents affecting Na excretion. Thus, it seems likely that the "S" rats possess abnormal antinatriuretic humoral effects that reduce Na excretion in perfused kidneys.

Since hematocrit and colloid osmotic pressure can influence sodium handling by the kidney, they were measured in the blood from "S," "R" and Sprague-Dawley rats, which perfused the isolated kidneys. All three groups had similar hematocrit levels and similar levels of colloid osmotic pressure in the plasma, both before and after volume expansion. There was no significant difference between the three groups.

After the initial 15-minute collection period, the perfusing rats were expanded with a mixture of two-thirds rat blood and one-third Krebs' solution, infused over a 1-hour period at a rate of 5% of the body weight per hour. As seen in figure 4, during the last 30 minutes of this 60-minute expansion period, the isolated kidneys increased twofold their output of Na, indicating the appearance of circulating natriuretic humoral agents in response to the stimulus of volume expansion. These natriuretic agents do not appear at all during control experiments in which there is no expansion. However, the "S" rats and the "R" rats showed about the same degree of enhanced natriuresis in response to volume expansion. The "S" rat did not appear to differ from the "R" rat in its ability to bring forth natriuretic hormones in response to volume expansion.

**Discussion**

The shift in the pressure natriuresis curve of the Dahl "S" rat could account in part for its great susceptibility to NaCl-induced hypertension. The fact that a thiazide diuretic, which acts primarily on the kidney to facilitate Na excretion, can prevent this NaCl hypertension is in agreement with and lends support to this hypothesis.

There are no obvious pathological lesions in the "S" kidneys to account for the shift in the pressure-natriuresis curve. This leads one to consider hormonal or nerve-borne influences on the "S" kidney that could explain its shifted natriuresis curve. In these studies, there appear to exist humoral agents in the blood of prehypertensive "S" rats on a 0.3% NaCl diet, which can induce a neutral bioassay kidney to halve its rate of Na excretion. There are also humoral agents in the blood of "S" rats that can induce a 16% increase in renal vascular resistance in a neutral bioassay kidney. However, it was apparent that the reduced Na excretion was not dependent on the increase in renal vascular resistance. However, this renal vasoconstric-
tion would be expected to enhance the reduction of Na excretion induced by the anti-natriuretic humoral agents. The fractional excretion of Na was also reduced by 50% in the neutral bioassay kidney perfused with "S" blood. When groups of "S" and "R" perfusions were selected to equalize GFR in the two types of perfusions, it was apparent that the Na excretion was still about 40% lower in the "S" perfusions compared to "R" perfusions. This finding suggests that humoral agents were ultimately increasing sodium reabsorption in the renal tubules, although their influence on the tubule could be either direct or indirect. The humoral agents cause a reduction of urine flow as well as a reduction of Na excretion. When normal Sprague-Dawley rats were compared with "S" and "R" rats, it was apparent that the anti-natriuretic effect of "S" blood was not seen in the blood of Sprague-Dawley rats, whereas the blood from "R" rats and from Sprague-Dawley rats had similar humoral effects on the neutral bioassay kidney. The results in these non-expanded rats actually indicate that perfused "S" blood has a greater humoral anti-natriuretic effect than "R" blood or Sprague-Dawley blood. This could be accounted for by abnormal amounts of anti-natriuretic humoral agents in "S" blood. It could alternatively be explained if "S" blood were lacking in natriuretic hormones which were abundantly present in "R" blood and in Sprague-Dawley blood. It seems likely that the anti-natriuretic effects in "S" rats could reduce Na excretion in the bioassay kidney by at least three mechanisms: 1) renal vasoconstriction causing a reduced renal blood flow; 2) a reduction in GFR, and 3) a direct or indirect action on renal tubules to enhance sodium reabsorption. Moreover, the studies of volume expansion indicated that both "S" and "R" rats were equally able to bring out natriuretic humoral agents in response to the volume expansion stimulus.

If the anti-natriuretic humoral agents circulating in the blood of "S" rats have an effect that lasts as long as 30 minutes, they could partially account for the shift in the pressure-natriuresis curve of the isolated "S" kidney. The same humoral agents may be involved in causing the 26% reduction in plasma flow to the renal papilla in Dahl "S" rats.14 These humoral agents may also relate to the pro-hypertensive humoral factors discovered by Iwai and Dahl in parabiosis experiments.15,16 Although the kidney and adrenal glands are excluded as a source for the humoral agents, much more work needs to be done to find which organ in the body secretes these anti-natriuretic humoral agents.

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