ACIDIFICATION OF THE URINE AND INCREASED AMMONIUM 
EXCRETION WITHOUT CHANGE IN ACID-BASE EQUILIBRIUM: 
SODIUM REABSORPTION AS A STIMULUS TO THE 
ACIDIFYING PROCESS 1, 2

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Acidification of the urine and excretion of ammonium are commonly thought to be regulated by 
the acidity of body fluids in such a manner that the kidneys in effect defend the normal pH of 
body fluids. Acidosis in blood or tissues is thought to increase excretion of acid and am-
monium, and alkalosis to decrease it (1).

Data inconsistent with this view were first presented in 1923 by Hendrix and Sanders (2) who 
found that administration of alkaline sodium phosphate or sodium hippurate to fasting, slightly acid-
otic dogs increased the acidity of the urine and the excretion of ammonium, despite the fact that the 
blood bicarbonate concentration rose. In 1934, Briggs (3) observed that administration of so-
dium sulfate to dogs increased renal excretion of ammonium and decreased excretion of titratable 
al kali. Sodium sulfate produced similar but less striking changes in normal men. Although Briggs 
did not measure blood bicarbonate or pH, and therefore did not rule out a slight acidosis due to 
dilution, he concluded that excretion of ammonium was a response to increased acidity of the urine 
and was independent of the acidity of the blood. He left unexplained the fundamental question, 
why infusion of a neutral salt like sodium sulfate or an alkaline substance such as dibasic phosphate 
should acidify the urine.

Pitts has adduced evidence that the urine is acidified by a process of ion exchange of sodium 
for hydrogen (4). Through this mechanism at least some part of sodium reabsorption is linked to 
the acidification of the urine. In the light of this concept it was decided to ascertain whether, 
by varying the stimulus to sodium reabsorption, it would be possible to affect the acidity of the 
urine without first changing the acidity of the body fluids. The experiments to be described below 
answer this question affirmatively. They also suggest an explanation for the observations of Hen-
drix and Sanders, and of Briggs, as well as the more recent data which indicate that urine am-
monium or acid excretion may be conditioned by factors other than body acidity (5, 6).

METHODS

The response to a standard alkaline sodium sulfate in-
fusion was studied in fourteen experiments on nine healthy adult male subjects. Two groups of experiments were 
carried out with this standard infusion. In seven con-
trol studies subjects had been allowed to eat a normal 
diet prior to the morning of the experiment. On un-
measured, but presumably average, intakes of sodium, 
their urinary excretion of sodium in the control periods 
only to infusion of sulfate ranged from 212 to 436 micro-
equivalents per min. In the other seven studies, renal 
conservation of sodium had been induced prior to the ex-
periment by one or more of several expedients aimed at 
stimulating reabsorption of this ion. Four subjects had 
been on a low-sodium diet (approximately 10 mEq. so-
dium per day by calculation) for four to six days prior 
to the experiment, and had received 2 cc. of a mercurial 
diuretic on each of the first two days of the period of 
sodium restriction. Two of these subjects were also 
given 200 mgm. per day of compound F acetate by 
mouth in four equal doses on the day before, and the day 
of, the experiment. In order to stimulate sodium reab-
sorption without concomitant sodium depletion, the re-
maining three subjects were allowed a normal diet, but 
one was given desoxycorticosterone acetate (15 mgm. 
intramuscularly twice daily) and the other two were 
given compound F acetate (300 mgm. daily by mouth in 
four equal doses) for a similar two-day period. As a 
result of these procedures, sodium excretion in the seven 
experimental subjects was markedly reduced during the 
urine collection periods prior to sulfate infusion. The sub-

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jects on low-sodium diets excreted 2 to 11 microequivalents per min. and those given only adrenal steroids excreted 60 to 79 microequivalents per min.

All experiments were carried out in the morning with the subjects fasting and supine. Water was taken by mouth at a rate of 100 cc. every half hour to insure adequate urine flows. At intervals of one-half hour the subjects voided directly into graduated cylinders partly filled with neutral mineral oil. Venous blood was drawn into oiled syringes at appropriate intervals.

After two or three control periods, one liter of approximately 0.2 N sodium sulfate solution was infused intravenously over a 30 to 40-minute period. Thirty to thirty-five mEq. of sodium bicarbonate were added to each infusion in order to avoid any acidifying effect from dilution. Collections of urine and blood were continued for two and a half or three hours after the start of the infusion.

Concentrations of sodium, potassium, carbon dioxide, and chloride of serum, and pH of whole blood were measured. Urine specimens were analyzed for pH, titratable acidity, ammonium, sodium, potassium, chloride, phosphate, and carbon dioxide. These methods have been described previously (7). In addition to these determinations all urine samples were analyzed for endogenous creatinine (8) and the specimens collected after the sulfate infusions were analyzed gravimetrically for sulfate (9). Urine bicarbonate was calculated from the pH and concentration of carbon dioxide, using the Henderson-Hasselbalch equation.

**RESULTS**

Typical experiments are shown in Tables I and II. The subject of Table I received a normal diet; the subject of Table II was taking a low-sodium diet and compound F acetate.

**TABLE I**

*Control experiment—Experiment 7, E. F.—Normal diet*

<table>
<thead>
<tr>
<th>Time (min.)</th>
<th>Serum</th>
<th>Urine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>pH at 37°C</td>
<td>CO₂ mEq/L</td>
</tr>
<tr>
<td>0-30</td>
<td>7.37</td>
<td>29.0</td>
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<tr>
<td>30-60</td>
<td>7.41</td>
<td>28.1</td>
</tr>
<tr>
<td>60-100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60-90</td>
<td>7.39</td>
<td>29.8</td>
</tr>
<tr>
<td>90-120</td>
<td>7.40</td>
<td>29.6</td>
</tr>
<tr>
<td>120-150</td>
<td>7.41</td>
<td>29.5</td>
</tr>
<tr>
<td>150-180</td>
<td>7.42</td>
<td>29.4</td>
</tr>
<tr>
<td>180-210</td>
<td>7.44</td>
<td>29.2</td>
</tr>
<tr>
<td>210-240</td>
<td>7.39</td>
<td>29.7</td>
</tr>
</tbody>
</table>

Infuse 1,000 cc. containing 190 mEq. Na₂SO₄ and 32 mEq. NaHCO₃

**TABLE II**

*Sodium-retaining subject—Experiment 14, R. J.—Low-sodium diet, compound F acetate*

<table>
<thead>
<tr>
<th>Time (min.)</th>
<th>Serum</th>
<th>Urine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>pH at 37°C</td>
<td>CO₂ mEq/L</td>
</tr>
<tr>
<td>0-30</td>
<td>7.39</td>
<td>29.3</td>
</tr>
<tr>
<td>30-60</td>
<td>7.43</td>
<td>29.7</td>
</tr>
<tr>
<td>60-100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60-90</td>
<td>7.44</td>
<td>28.7</td>
</tr>
<tr>
<td>90-120</td>
<td>7.44</td>
<td>28.7</td>
</tr>
<tr>
<td>120-150</td>
<td>7.44</td>
<td>28.7</td>
</tr>
<tr>
<td>150-180</td>
<td>7.44</td>
<td>28.7</td>
</tr>
<tr>
<td>180-210</td>
<td>7.44</td>
<td>28.7</td>
</tr>
<tr>
<td>210-240</td>
<td>7.45</td>
<td>30.9</td>
</tr>
</tbody>
</table>

Infuse 1,000 cc. containing 201 mEq. Na₂SO₄ and 34 mEq. NaHCO₃
Changes in the serum

Infusion of the mixture of sodium sulfate and sodium bicarbonate produced no significant change in blood pH or serum carbon dioxide content in either subject. Serum sodium and chloride also remained essentially unchanged. Potassium decreased sharply in the subject on the low-sodium diet (Table II), but decreased slightly, if at all, in the normal subject (Table I).

Changes in the urine

Infusion of approximately equal quantities of sulfate resulted in prompt and roughly equal excretion of the loading anion. The maximum excretion of sulfate was 1405 microequivalents per min. in the control subject and 1320 microequivalents per min. in the other. Total excretion of sulfate during the period of observation was 131 mEq. in each instance. Chloride excretion fell off sharply. In the sodium-retaining subject chloride excretion, already very low in the pre-infusion periods, was virtually obliterated. Two other points of similarity were noted: a) in both subjects phosphate excretion was negligible and essentially unchanged, and b) endogenous creatinine clearances remained relatively stable throughout both experiments.

The significant differences between the control and experimental subjects occurred in the urine pH and in the excretion of bicarbonate, ammonium, sodium, and potassium:

a) Urine pH did not change significantly in the control subject (if anything, it may have risen slightly), but in the experimental subject there was a sharp drop in pH which reached a minimum of 4.3 in the second and third half-hour periods following completion of the infusion.

b) As might be expected from the striking differences in urine pH, bicarbonate excretion did not change significantly in the control experiment, but in the other experiment it virtually ceased.

c) Ammonium excretion was essentially unaffected by the sulfate infusion in the control subject, but increased by a maximum of 49 microequivalents per min. in the experimental subject.

d) Sodium excretion was greatly augmented in both experiments, but the maximum increment was greater by 265 microequivalents per min. in the control subject.

e) Potassium excretion was also significantly increased in both experiments, but the increment was greater in the experimental subject. In this particular experiment the increment in potassium excretion preceded by two periods the sharp fall in pH and rise in ammonium excretion.

Differences between the urinary responses of the groups

Urine pH: Figure 1 illustrates the response of urine pH in both groups. The control subjects are represented by open circles and the experimental subjects by solid dots. It will be noted that the average urine pH in the periods prior to infusion of sulfate was in the same range (6.3 to 7.3) in both groups of subjects. The minimum pH after the infusion ranged between 6.0 and 6.8 in the seven control experiments; in five subjects the change in pH represented a slight decrease and in two subjects a slight increase. The urine pH in the experimental group always fell sharply, the minimum pH following the infusion ranging from

![Graph showing the effect of sodium sulfate infusion on urine pH](image-url)
5.2 to 4.0. The four subjects on low-sodium diets had the most acid urines during the experimental periods and the lowest sodium excretions (2 to 11 microequivalents per min.) during the control periods; the other three subjects, who excreted 60 to 79 microequivalents per min. of sodium during control periods, had less acid urines. The acidification of the urine in response to sulfate infusion, therefore, appeared to be dependent not only upon the existence, but also upon the intensity, of the tendency to reabsorb sodium.

Ammonium excretion: Table III presents the data on total cumulative increments in ammonium excretion for the first two-and-a-half hours after the start of the infusion. The mean increment in ammonium excretion in the control group was 823 microequivalents, and in the sodium-retaining group 3639 microequivalents. The difference between these means was highly significant (p < .01). Figure 2 illustrates the differences between the two groups with respect to the maximum increase in urine ammonium excretion produced by the sulfate infusion in a single period. The mean increment in the control group was 8 microequivalents per min. (range: 0 to 17 microequivalents per min.), while the mean increment in the experimental group was 42 microequivalents per min. (range: 24 to 69 microequivalents per min.). These differences, when tested statistically, are highly significant (p < .01).

Potassium excretion: Table IV presents the data on total cumulative increments in potassium excretion for the five half-hour periods after the start of the infusion. The mean increment in total potassium excretion in the control group was 2618 microequivalents and in the sodium-retaining group 21,514 microequivalents. The difference between these means was highly significant (p < .01).

Serum potassium decreased in approximate proportion to the magnitude of the potassium excretion in the urine. The largest reduction in concentration (1.1 mEq. per L.) was found in

![Figure 2: The Effect of Sodium Sulfate Infusion on Urine Ammonium Excretion](image)

**TABLE III**

<table>
<thead>
<tr>
<th>Control group</th>
<th>Experimental group</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1,380</td>
</tr>
<tr>
<td>2</td>
<td>1,440</td>
</tr>
<tr>
<td>3</td>
<td>780</td>
</tr>
<tr>
<td>4</td>
<td>30</td>
</tr>
<tr>
<td>5</td>
<td>2,130</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Mean</td>
<td>823</td>
</tr>
<tr>
<td>S.D.</td>
<td>855</td>
</tr>
</tbody>
</table>

**TABLE IV**

<table>
<thead>
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<th>Control group</th>
<th>Experimental group</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4,410</td>
</tr>
<tr>
<td>2</td>
<td>1,560</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>1,950</td>
</tr>
<tr>
<td>6</td>
<td>1,110</td>
</tr>
<tr>
<td>7</td>
<td>9,270</td>
</tr>
<tr>
<td>Mean</td>
<td>2,618</td>
</tr>
<tr>
<td>S.D.</td>
<td>3,294</td>
</tr>
</tbody>
</table>
the subject in Table II, who lost the greatest
amount of potassium in his urine.

Titratable acid: While there appeared to be a
slight increase in titratable acid in some of the ex-
perimental subjects (see Table II), the small
amount of buffer (phosphate) present in the urine
and the variations in its rate of excretion make the
titratable acid data difficult to interpret. For this
reason, no further comment on this subject will be
made.

DISCUSSION

According to present concepts the urine is acid-
ified, probably in the distal convoluted tubules, by
a process involving exchange of sodium for hydro-
gen ions (4). Substitution of hydrogen for so-
dium converts bicarbonate in tubular fluid to car-
bonic acid and lowers the pH. It also increases
titratable acidity of the urine by an amount deter-
mined by the final pH and the quantity and pK of
each of the buffer substances excreted in the urine.

Although acidification of the urine is widely be-
lieved to be a response to increased acidity of the
blood or tissues, this hypothesis could not explain
the results of the present experiments. Since all
of the subjects received the same, slightly alkaline
infusion, and since carbon dioxide and pH of
serum did not change significantly in any of the
subjects, it is not likely that the increased urine
acidity following the infusion of sodium sulfate in
the experimental subjects was the result of acidi-
fication of either extracellular or intracellular
fluid. These experiments therefore indicate that
the acidifying response to the sulfate load was con-
tioned by the tendency to retain sodium which
existed prior to the administration of the load.

To explain how the state of sodium metabolism
was responsible for the differences in urine acidity
between the control and experimental groups, it is
suggested that, in general, acidification of the urine
will occur whenever there is a strong stimulus for
increased reabsorption of sodium during the ob-
ligatory excretion of anion. Loading with the so-
dium salt of a relatively unabsorbable anion like
sulfate increases delivery of sodium and sulfate
to the tubular site where the acidifying process of
sodium-hydrogen exchange occurs. When there
exists a strong stimulus for sodium reabsorption,
such as that produced in the experiments reported
here, the sodium sulfate load produces a sudden
acceleration of the exchange process. That moity
of the sodium load reabsorbed without simultane-
ous reabsorption of anion obviously must be re-
placed in the tubular fluid by hydrogen or some
other cation, such as potassium or ammonium.

The amount of hydrogen substituted for a given
amount of reabsorbed sodium is probably limited
by the amount of buffer substances (free am-
monia and dibasic phosphate) available to “ac-
cept” the hydrogen, and by the limiting concen-
tration of free hydrogen ions which can be achieved
in tubular fluid. Since maximum acidity was
achieved in those subjects in whom the stimulus
for sodium reabsorption (as measured by the con-
trol sodium excretion) was strongest, it would
seem that, under standard conditions of anion ex-
cretion, the intensity of the stimulus to sodium
reabsorption influences the final urine pH. Vary-
ing effects of sodium sulfate loads on urine pH
reported by other workers (11, 12) are therefore
probably explained by differences in the sodium-
retaining tendencies of their subjects.

Differences in ammonium excretion between the
control and experimental groups were striking
(Figure 2, and Table III). It has been suggested
that the acidity of the urine determines ammonium
excretion (3, 4) and it is possible that the marked
reduction in the urine pH in the experimental
subjects was the immediate cause of their aug-
mented ammonium output. Under standard con-
ditions there tends to be an inverse relation be-
tween urine pH and ammonium excretion, but it is
generally conceded that urine pH is not the sole
determinant of ammonium excretion since the
latter may vary independently of urine pH (4).
Regardless of whether or not one believes that the
ammonium excretion is the direct consequence of
the increased urine acidity, the fact remains that
in the present experiments the initiating stimulus
to urine acidification and ammonium excretion
must have been those factors which increased re-
absorption of sodium in excess of anion, and they

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8 While it is recognized that a small error may be in-
troduced by the measurement of urine pH at room tem-
perature, and the use of a correction factor of .01 pH
units per degree Centigrade (10), it is nevertheless worthy
of note that the minimum values observed in three ex-
perimental subjects were 4.3 or below. To our knowl-
edge, acidity of this degree has not previously been re-
ported in human subjects.
apparently were not related to any change in acidity of body fluids. This conclusion does not exclude the possibility that there may also be other physiologic stimuli to ammonium excretion; nor should it obscure the probability that for any given stimulus the absolute magnitude of ammonium excretion may be modified by other factors, including the availability of amino acid substrate (13), the activity of tubular deaminating systems (14), and possibly the presence of other buffers in the urine.

Both groups of subjects excreted more potassium following the sulfate infusion but the mean cumulative potassium loss in the experimental group was considerably larger than in the control (Table IV). Regardless of whether the potassium which appears in the urine is secreted in exchange for reabsorbed sodium (15) or whether it represents filtered potassium which is not reabsorbed, the markedly increased potassium excretion in the experimental group was clearly related to the accelerated sodium reabsorption. The small potassium diuresis observed in most of the control subjects, as well as the occasional small increments in urine acidity and ammonium excretion, may have been due to slight increases in sodium reabsorption resulting from the sodium load (16), although some non-specific effect of the sulfate ion, or the influence of diurnal variation cannot be ruled out.

Presumably the increment in potassium excretion constitutes another sodium-sparing mechanism, similar in this respect to the increased sodium-hydrogen exchange which resulted in augmented excretion of ammonium and increased urine acidity. Comparison of Tables III and IV shows that in these experiments potassium excretion is quantitatively more important as a sodium-conserving mechanism than is excretion of ammonium. The temporal relationships among these sodium-exchange processes are variable. In some experiments (e.g., Experiment No. 10, Figure 3) all three mechanisms appeared to be activated simultaneously in the first post-infusion period. In other experiments (e.g., Experiment No. 14, Table II) following the infusion there were one or more periods of potassium diuresis before the first sharp drop in urine pH.

The relationship suggested here between sodium reabsorption and the excretion of ammonium, free hydrogen, and potassium would seem to explain many earlier observations, including those of Hendrix and Sanders (2), and Briggs

![Figure 3](image-url)

**Fig. 3.** Changes in Excretion of Potassium and Ammonium, and in Urine pH, Produced by Infusion of Sodium Sulfate in a Sodium-Retaining Subject (Experiment No. 10)

The shaded area denotes the period of infusion. Note that, following this, urine pH drops simultaneously with rise in potassium and ammonium excretion.
(3). Renal conservation of body sodium requires tubular reabsorption of most of the filtered sodium under all circumstances. The tendency for sodium to be retained whenever its salts are administered probably explains why loading with rapidly excreted anions such as phosphate (2, 17), hippurate (2), para-aminohippurate (18), or sulfate (3) results in increased excretion of potassium, ammonium or acid. The contribution of titratable acid to the sodium-sparing process will depend upon the amount of urinary buffer available. Increasing the stimulus for sodium reabsorption will increase the activity of these mechanisms. Under these circumstances even sodium chloride loading might be expected to result in increased urine acidity and ammonium excretion, as was observed by Ryberg (19). Active stimulation of sodium reabsorption in excess of anion probably explains why prior depletion of sodium accelerates the renal ammonium and potassium responses to loading with acid salts, and why the magnitude of this response is not necessarily related to the degree of extracellular acidosis or to the quantity of acid retained in the body (6).

It may be postulated that the acute potassium diuresis in the sodium-retaining subjects resulted in loss of potassium from renal tubular cells and that this was a factor in the increased acidity of the urine (15). This possibility cannot be excluded in some experiments, but the occurrence in other experiments (Figure 3) of simultaneous increments in potassium, ammonium, and free hydrogen makes this hypothesis unlikely. Furthermore, the acidity of the urines in most of these experiments is much more marked than in any of those reported in clinical or experimental potassium depletion (20–22), even in cases where total potassium losses were far larger than those produced here.

A final point of interest is that the sulfate infusion tends to diminish chloride excretion in both groups of subjects but it affects bicarbonate in only the experimental group. If there is any competition among the inorganic ions for priority in reabsorptive transport (23), bicarbonate appears not to participate.

SUMMARY AND CONCLUSIONS

An alkaline infusion of sodium sulfate was administered rapidly to a control group of subjects and to subjects previously stimulated to retain sodium by sodium-free diets, adrenal steroids, or both. Although there were no significant changes in blood pH or CO₂ content, the urine of the sodium-retaining group became intensely acid, ammonium excretion increased, and there was a striking increase in the excretion of potassium. Despite an equivalent excretion of sulfate, the control group showed no consistent or significant change in urine pH or ammonium excretion and only a small increment in potassium excretion.

It is concluded that a stimulus to reabsorb sodium without equivalent amounts of anion will result in acidification of the urine and increased ammonium and potassium excretion. This response does not require any prior change in acidity of blood or tissues. The degree of urine acidity achieved is approximately proportional to the intensity of the stimulus to sodium reabsorption.

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REFERENCES


