Cation Uptake by Exchange Resin in Vitro and the Colon as a Sodium-Conserving Organ

By Henry Field, Jr., M.D., Leon Swell, Ph.D., D. F. Flick, M.S., and Robert E. Dailey, M.S.

Cation-exchange resins have not fulfilled early expectations. Those in clinical use do not retain much sodium in the feces when dietary sodium is much restricted. Comparison of the sodium and potassium bound by a resin, in equilibrium with presumably normal electrolytes as found in the terminal ileum, with the amounts of those ions in the feces, permits an over-all evaluation of two major factors operating in the gastrointestinal tract. These are a decreased sodium concentration in the terminal ileal contents when sodium intake is restricted and an absorptive power of the colon sufficient to detach sodium from the resin.

It has been a consistent observation that cation-exchange resins will retain much more sodium in the feces of experimental animals or patients who are consuming diets with a liberal sodium content than when dietary sodium is much restricted. When subjects have been maintained on diets with unrestricted sodium intake, a carboxylic cation-exchange resin similar to the one used in this study has been found to retain in the feces 0.5 to 2.5 mEq. of sodium and 0.4 to 2.9 mEq. of potassium per gram of resin. When diets containing between 500 and 800 mg. of sodium per day were consumed the resin has bound, in the feces, 0.26 to 0.80 mEq. of sodium and 0.27 to 2.32 mEq. of potassium per gram of resin.

The reason for these differences in the amount of sodium fixed by the resin in the feces when subjects are taking liberal and low sodium diets has been obscure. There is, normally, a large amount of sodium in the secretions of the gastrointestinal tract, to which the resin is exposed. It has been suggested that “endogenous” sodium does not combine with cation-exchange resin in the intestinal tract and that the sodium removed in the feces by the resin is “exogenous” sodium of dietary origin.

It is difficult to understand why the resin should react differently with sodium of different origins. It has seemed necessary to seek a better explanation for the seemingly different behavior of the resin to “exogenous” and “endogenous” sodium. The uptake of cations by exchange resins depends upon the following factors: (a) concentration of ions, (b) pH of the medium, (c) the relative affinity of the resin for different cations and (d) the concentration of resin.

In the gut, there are other possible mechanisms that might effect the uptake of sodium by exchange resins. One is the previously unexplored possibility that the sodium concentration of the contents of the ileum may become decreased when the sodium content of the diet is much restricted. McCance reported a decreased sodium content of gastric juice, saliva and sweat in subjects who were maintained on low sodium diets. Studies which are in progress, utilizing dogs with ileal fistulas, indicate that the concentration of sodium in the terminal ileum is considerably decreased during sodium deprivation.

There is also the possibility of absorption of sodium by the colon, against the gradient of the affinity of the resin for it. Whether there is an active absorption of ions from the gut or whether their absorption is by a simple process of diffusion has long been a subject of controversy. In most of the large volume of experimentation concerning intestinal absorption, loops of the small bowel have been used. The intestinal contents normally reach the terminal ileum with their electrolytes approximately in equilibrium with those of the plasma.
though a rather wide range of values has been reported by Lockwood and Randall. In contrast, there is relatively little sodium in the feces. In agreement with that, the preponderance of evidence from direct experiments with loops of colon, reported by Goldschmidt and Dayton and Visscher and his associates, is indicative of active absorption, against osmosis, by the colon. Among others, Odell and Ferris have successfully used a solution in approximate electrolyte equilibrium with the plasma for dialyzing lavage of the small intestine in the treatment of renal insufficiency. However, when they used the same solution for dialyzing lavage of the colon, of 40.5 liters of solution run in through an appendicostomy tube in 64 hours, only 24.5 liters were recovered through the rectal tube and their patient became edematous. There has been, thus, abundant evidence of active absorption of electrolytes by the human colon. It remains to be determined if the power of the human colon to absorb electrolytes is sufficient to affect the retention of sodium in the colon by cation-exchange resins.

There has also been evidence that absorption of electrolytes is subject to hormonal influence. Dennis and Visscher found that excitement was associated with a decreased rate of absorption from loops of the ileum in the trained unanesthetized dog. Anesthetization of excited dogs increased the rate of absorption, while anesthetization of placid dogs caused no such change. Dennis and Wood found that adrenalectomized dogs, maintained on high sodium, high bicarbonate and low potassium diets, had a marked decrease in the rates of absorption of sodium, potassium and chloride from the ileum. This was reversed in each instance following the administration of adrenal cortical extract. When the cortical extract was withdrawn, the rate of sodium absorption in general declined more than that of potassium. At times there seemed to be an actual reversal in the direction of movement of sodium with excretion of it into the intestinal tract in relatively large amounts, although potassium was still being absorbed. Leaf and Couter found indirect evidence of changes in adrenal-cortical activity, in normal human subjects, associated with changes in the salt content of their diets. Berger, Quinn and Homer reported that desoxycorticosterone acetate (DOCA) decreased the fecal excretion of sodium in rats and also in human subjects. In another study, Berger and Steele reported that less sodium was retained in the feces of edematous cardiac and cirrhotic patients, by cation-exchange resin, than in control subjects.

In this study, the sodium and potassium fixed by a carboxylic cation-exchange resin* exposed, in vitro, to a solution containing approximately the electrolyte concentrations of the contents of the terminal ileum, as reported by Lockwood and Randall, have been determined and compared with the amounts of those ions per gram of resin present in the feces of patients.

**METHODS AND MATERIALS**

*In vivo experiments.* Five male patients were used in these studies. The patients were compensated cardiacs on low sodium diets and were receiving no diuretic medication other than digitalis. The diets were prepared under the direction of the hospital dietitian and contained 0.8 to 1.2 Gm. of sodium per day. The diets were restricted in potassium to the extent of omitting fruit juices and salt substitutes. Forty-five Gm. of carboxylic cation-exchange resin in the ammonium and potassium form (ratio of one part potassium to two of ammonium) were fed daily to each patient except patient Ly who received the hydrogen cycle form of the resin, as will be explained. The resin was given in three 15 Gm. doses in water daily following meals.

Feces were collected daily in cardboard containers, using carmine dye as a marker, pooled for analysis, and mixed by an electric mixer into three-day specimens. Twenty-four hour urine samples were collected daily and blood samples were taken every three days for determinations of their sodium and potassium contents.

The feces samples were weighed out in crucibles, four-normal sulfuric acid added and the samples heated on a hot plate to dryness. The residue was ashed in a muffle furnace at 550 C. overnight. The ash was dissolved in hydrochloric acid and analyzed for sodium and potassium content. The sodium and potassium determinations were carried out on the Barclay flame photometer with an internal lithium standard. The sodium and potassium con-

* Resodec and its equivalent in the hydrogen cycle form were kindly supplied by the Smith, Kline and French Company.
tents of urine and serum were determined directly after appropriate dilution. 

In vitro experiments. A mixture of sodium chloride, sodium hydroxide and potassium chloride which had approximately the average ionic concentration of the contents of the terminal ileum as reported by Lockwood and Randall, was equilibrated with known amounts of cation-exchange resin in the hydrogen-cycle form. The solution had the following composition: 129.4 mEq. per liter of sodium as sodium chloride and sodium hydroxide, 11.2 mEq. per liter of potassium as potassium chloride and 116.2 mEq. per liter of chloride as potassium chloride and sodium chloride. The solution was made up in Aminosol (protein hydrolysate) to give a final concentration of 2.5 per cent of the hydrolysate.

The resin was weighed out, mixed with 1000 cc. of the solution, and shaken for one hour on a shaking machine. The pH of the solution was determined before exposure to the resin and then after shaking. The mixture was filtered and the resin was dried overnight at 100 C. The resin was analyzed for sodium and potassium after ashing. Experiments were conducted in which the supernatant, washed and unwashed resin were analyzed. Analysis of the supernatant introduced considerable error due to the large dilution while direct analysis of the washed or unwashed resin gave consistent results; there was no significant loss of sodium or potassium when the resin was washed.

RESULTS AND DISCUSSION

In Vitro. It will be seen in table 1 that only 1 or 2 Gm. of the carboxylic resin, in the hydrogen cycle, could be equilibrated with 1 liter of the solution without lowering its pH below the physiologic range encountered in the terminal ileum. As the solution became increasingly more acid with increasingly large amounts of the resin, there was a progressive decrease in the total uptake of cations per gram of resin. However, the findings of Karr and Abbott concerning the contents of the ileum, obtained by a Miller-Abbott tube after feeding of hydrochloric acid, indicate that the hydrogen-ions released from the resin, when it is taken therapeutically, would be absorbed in passage. Consequently, it would appear that, with the proportionately larger amounts of resin used in the in vivo experiments, the final equilibrium in the terminal ileum would have been at the normal pH. Thus, the uptake of cations per gram of resin, in the terminal ileum during the intestinal passage in patients would be expected to be that found in these experiments at the final pH values of 7.1 and 6.8. That was 2.79 and 2.34 mEq. of sodium, respectively, and 0.18 mEq. of potassium per gram of resin. (This does not allow for the probability that the concentration of sodium in the terminal ileum may be decreased during sodium depletion.) The sodium to potassium ratio under these conditions was 7:1.

In Vivo. The sodium and potassium contents per gram of resin in the feces of five patients, representing 211 patient-days of resin administration, was quite different from the uptake of cations under the conditions existing in the terminal ileum as indicated by the in vitro experiments. This is shown in table 2 and in table 3. In the latter table the average fecal sodium for the entire group, over that period of time, is contrasted with the uptake by the resin when in equilibrium in a solution with the

<table>
<thead>
<tr>
<th>Amt. Resin Gm./L.</th>
<th>Initial pH</th>
<th>Final pH</th>
<th>Na Cation Uptake</th>
<th>K Cation Uptake</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7.5</td>
<td>7.1</td>
<td>2.79</td>
<td>0.18</td>
</tr>
<tr>
<td>2</td>
<td>7.5</td>
<td>6.8</td>
<td>2.34</td>
<td>0.18</td>
</tr>
<tr>
<td>4</td>
<td>7.5</td>
<td>6.3</td>
<td>1.52</td>
<td>0.12</td>
</tr>
<tr>
<td>8</td>
<td>7.5</td>
<td>5.7</td>
<td>0.88</td>
<td>0.08</td>
</tr>
<tr>
<td>10</td>
<td>7.5</td>
<td>5.5</td>
<td>0.70</td>
<td>0.08</td>
</tr>
</tbody>
</table>

* The solution, before equilibration, contained the concentrations: Sodium, 129.4 mEq./L.; potassium, 11.2 mEq./L. and chloride, 116.2 mEq./L., which were the average values for those ions in the contents of recent ileostomies, as reported by Lockwood and Randall.*

<table>
<thead>
<tr>
<th>Patient</th>
<th>Days on Resin</th>
<th>Serum Na mEq./L.</th>
<th>Urine Na mEq./day</th>
<th>Feces Na mEq./day</th>
<th>Feces K mEq./day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Du.</td>
<td>48</td>
<td>3.9</td>
<td>13.9</td>
<td>46.2</td>
<td>18.3</td>
</tr>
<tr>
<td>St.</td>
<td>48</td>
<td>4.2</td>
<td>46.1</td>
<td>64.1</td>
<td>25.7</td>
</tr>
<tr>
<td>St.</td>
<td>48</td>
<td>4.2</td>
<td>39.1</td>
<td>67.0</td>
<td>12.8</td>
</tr>
<tr>
<td>Te.</td>
<td>48</td>
<td>4.2</td>
<td>39.1</td>
<td>67.0</td>
<td>17.4</td>
</tr>
<tr>
<td>Ly.</td>
<td>24</td>
<td>3.9</td>
<td>32.2</td>
<td>66.7</td>
<td>6.1</td>
</tr>
</tbody>
</table>

* All figures represent average values.
approximate electrolyte composition of the contents of the terminal ileum.

There was a considerable difference between different patients in the sodium content of their feces and, consequently, in the proportion of total sodium excretion which was renal. Ninety-seven and nine-tenths per cent of patient Sto's sodium excretion, neglecting sodium in sweat, was by his feces and he averaged only 0.6 mEq. of sodium per 24 hours in his urine. In contrast, patient Ly had only 15.9 per cent of his sodium excretion in his feces. It is possible that that difference in the amount of sodium retained in the feces by the resin in these patients was related to hormonal activity such as has been demonstrated in the experiments referred to.\textsuperscript{10-19} Patient Ly had malignant hypertension. He had been severely decompensated a few weeks before this experiment and he died a few weeks after its completion. Patient Sto was a normotensive with arteriosclerotic heart disease who for one and one-half years had been maintained in cardiac compensation only with the assistance of the resin or of mercurial diuretics.

Even patient Sto, who had the highest proportion of his sodium excretion by his feces, had only 0.63 mEq. of sodium per gram of resin in his feces. This is in contrast with the 2.5 mEq. of sodium per gram of resin which is the approximate amount which would have been bound by the resin when in equilibrium with the presumed contents of the terminal ileum during consumption of a normal diet.

It is to be noted that the colon does not absorb potassium as actively as it does sodium. In fact, the absorptive power of the colon for potassium is so weak that the cation-exchange resin, by its affinity for potassium, was able to withdraw from the colon average amounts, per patient, of potassium ranging from 28.2 mEq. in 24 hours for patient Te to 92.3 mEq. per 24 hours for patient Sto. Those are the average amounts of fecal potassium of those patients after deducting the 12.8 mEq. of potassium per 24 hours that is normally present in feces\textsuperscript{20} and the 8.1 mEq. of potassium that would have been bound by 45 Gm. of the resin in the terminal ileum, as indicated by the results of the in vitro experiments. In those experiments, it was found that the carboxylic cation-exchange resin bound only 0.18 mEq. of potassium under the conditions usually found in the terminal ileum. In contrast, the patients had each an average amount of potassium in their feces ranging from 0.71 to 2.50 mEq. (average for all periods of all patients, 1.52 mEq.) per gram of resin. The average ratio of sodium to potassium in all feces was 0.3:1, which contrasts with the ratio of 7:1, in the in vitro experiments.

Despite that large withdrawal of potassium in the feces, all of the patients had moderate to large amounts of potassium in their urines, as is indicated in table 2. Nevertheless, with the moderate restriction of potassium intake resulting from the omission of fruit juices and salt substitutes, all of the patients except Ly, who had potassium supplements throughout, suffered potassium depletion. The other four patients had declines in their serum potassium concentrations to 3.0 to 3.2 mEq. per liter before they were given potassium supplements. The figures for serum potassium given in table 2 are average values. Presumably, the patients would have experienced muscular weakness if their activity had not been limited. Tarail and Elkington,\textsuperscript{21} among others, have observed the continued urinary excretion of potassium by patients despite their having already suffered potassium deficiency. The withdrawal of potassium in the feces by exchange resins has been a concern to all investigators. Neither the colon nor the kidney are effective conservers of potassium.
Patient Ly had marked renal insufficiency with nitrogen retention. The resin, as it is marketed, would have been contraindicated because of its ammonia content and its acidifying potentiality. He tolerated the resin very well, in the hydrogen cycle, while its acidifying effect was neutralized by appropriate doses of potassium citrate.

There is to be considered the possibility of a decreased sodium concentration in the terminal ileum, due to the restriction of dietary sodium, which is inferred because of the finding by McCance of decreased concentrations of sodium in the saliva, gastric juice and sweat of patients subjected to a similar restriction of dietary sodium. However, assuming that its pH remained normal, the sodium concentration of the contents of the terminal ileum would have had to be reduced to 26.0 mEq. per liter for the resin, in equilibrium with it, to have bound only the 0.63 mEq. of sodium per gram of resin which was found in the feces of patient Sto. It would have had to have been reduced to 22.5 mEq. per liter (about one-sixth of the normal concentration) for the resin to have bound the 0.48 mEq. of sodium per gram of resin, which represents the average fecal sodium of all five patients, for 211 patient-days.

In our opening discussion, we have referred to the previous evidence that the colon is capable of active absorption of sodium against a concentration gradient, and that this absorption is subject to hormonal influence. The above data (table 3), comparing the amounts of sodium bound by this carboxylic resin when it is in equilibrium with electrolytes, as they have been found to occur in the contents of the terminal ileum, with the amount of sodium, per gram of resin, found in the feces is further evidence of the power of the colon to absorb sodium against a gradient. It can overcome the affinity of the resin for sodium sufficiently so that, in most patients, it detaches from the resin and absorbs a major portion of the sodium which should have been bound to the resin as it passed the terminal ileum.

Active absorption of sodium by the colon, together with the probable decreased sodium concentration in the terminal ileum of patients with a restricted dietary sodium, greatly impairs the ability of this carboxylic cation-exchange resin to augment the sodium depletion which is possible by dietary restriction alone. Perhaps, in many circumstances, that is fortunate. There have been several reports of the low salt syndrome in patients on low sodium diets, although dietary effects were usually augmented with mercurial diuretics. Patient Sto, with a rather moderate restriction of dietary sodium and customary doses of this resin, maintained a normal serum sodium, but only by a narrow margin. For many weeks his urinary sodium excretion averaged 12 mg. per 24 hours. A cation-exchange resin with a greater affinity for sodium at the pH existing in the colon would have been advantageous in the treatment of the other four patients. It would have been disastrous to patient Sto, without the advantage of laboratory control or the timely clinical recognition of the low salt syndrome.

A further concept is supported by these data. It would appear that the colon has a role in the conservation of sodium almost comparable, in many patients, with that of the kidney. From previously reported evidence this sodium conserving function of the colon appears to be subject to hormonal influence. Among our patients there was a wide variation in the absorptive ability of the colon to detach sodium from its bonds to the resin or, possibly, in the decreased concentration of sodium in their ileums. Experiments are in progress, using dogs with fistulas into their terminal ileums, to obtain direct information concerning the absorption of sodium from their colons during the feeding of the resin.

**Summary and Conclusions**

A carboxylic cation-exchange resin has been equilibrated in vitro with a solution so constituted that its electrolyte content approximated that which has been found in the contents of the terminal ileum. The resin in that equilibrium fixed much more sodium and much less potassium than was found, per gram of resin, in the feces of five patients over prolonged periods.

It appears that the colon has sufficient power to absorb sodium so as to overbalance the affinity of the resin for sodium. The colon has a role in the conservation of sodium which may be, in many patients, almost comparable to that of the kidney. The colon gives up large
amounts of potassium to the resin. Neither the colon nor the kidneys are effective conservers of potassium.

**Sumario Español**

Resinas de intercambio de cationes no han producido los resultados esperados. Aquellas en uso clínico no retienen mucho sodio cuando el sodio en la dieta se restringe mucho. Comparación del sodio y el potasio atado a la resina, en equilibrio presumiblemente con los electrólitos normalmente hallados en el fion terminal, con las cantidades de estos iones en las heces, permite una evaluación generalizada de los dos factores mayores operando en el tracto gastrointestinal. Estos son, una disminución en la concentración del sodio del contenido del fion terminal cuando hay restricción en la ingestión del sodio y el poder de absorción del colon suficiente para separar sodio de la resina.

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