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CATION EXCHANGE IN THE GASTRO-INTESTINAL TRACT

BY

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Cation-exchange resins are surprisingly inefficient at removing sodium from the gastro-intestinal tract. It had been anticipated from *in vitro* studies (Morton, 1951) that the large preponderance of sodium over other cations in the fluids of the small intestine would more than compensate for the greater affinity which such resins exhibit for potassium. In practice, when cation-exchange resins are administered to patients on a low-salt diet they remove far more potassium than sodium (Dock and Frank, 1950; Barker and Mackay, 1951; Greenman *et al.*, 1951). It has been suggested, therefore, that exchange resins extract sodium only from the diet, their activity being confined to the upper small intestine (Hegsted *et al.*, 1951). This concept is opposed by McChesney (1952) and seems to be at variance with the physical and chemical properties of the resins.

Despite the abundance of clinical and experimental studies there appears to be little direct evidence concerning the action of ion-exchange resins at various levels in the intestinal tract. Data of this kind have been obtained in the present investigation. The rates of turnover of sodium and potassium ions to and from the exchange resin have also been measured with the radioactive tracers Na^{24} and K^{42} . From these results the activity of cation-exchange resin has been interpreted

in terms of a constantly changing series of dynamic equilibria between the cations on the resin and those in the intestinal fluids. Through this medium all the cations in the body continually exchange with those on the resin. The activity of the exchange resin is not confined to one region of the intestinal tract. On the contrary, cation exchange is continuous throughout the length of the gut. The rates of turnover of cations to and from the resin are not constant, however, but undergo a regular sequence of change as the resin passes from the stomach onwards to the rectum. One result of this complex cycle of activity is that when cation-exchange resins are administered in the ammonium or hydrogen phase there is a predominant uptake of sodium in the small intestine. Most of this sodium is exchanged for potassium and other ions in the colon.

Materials and Methods

These have largely been described in the previous paper (Spencer and Lloyd-Thomas, p. 597 of this issue). The resin used in these studies was a sulphonated polystyrene of equivalence 3.1 mEq per g. of resin. The phase and mesh size is given separately in the accounts of the individual experiments.

The total electrolyte contents of the stools, intestinal contents, and enema samples were obtained by flame photometry of dilute solutions prepared from ashed aliquots of the entire specimen. The resin was isolated by flotation from aliquots of the homogenized intestinal fluid. This was facilitated by administering part or all of the resin as a coarse (40–80 mesh) powder. The resin so obtained was dried at 60° C and weighed. The cations were eluted with 4N HCl and estimated as before. The radioactivity of the acid extract was determined in a liquid counter.

Composition of Ion-exchange Resin in the Small and Large Intestines

Samples of fluid and exchange resin were obtained from the small intestine by Miller-Abbott tube (2), from a fresh ileostomy (7), and at post-mortem examination from three patients who had died suddenly from coronary thrombosis (2) or pulmonary embolism (1). In the necropsy studies samples were also taken from the proximal colon and rectum. The subjects had all been taking a low-salt diet and a cation-exchange resin, as previously described by Spencer and Lloyd-Thomas at p. 597. Their plasma sodium concentrations were in the range 137–141 mEq per litre.

Results.—Resin taken from the small intestine had a similar composition in all the subjects. The results of these analyses, together with those for the resin from the colon, are summarized in Fig. 1. From these data it was apparent that the exchange resin had taken up large amounts of sodium in the small intestine even though the patients were on a low-salt diet. In the distal part of the colon there was more potassium bound to the resin than sodium, while

FIG. 1.—Mean concentration and relative proportions of sodium and potassium ions bound to a cation-exchange resin at different levels of the human gastrointestinal tract.

in the proximal colon the composition of the resin was intermediate between these two. These results suggested that most of the sodium ions taken up by the resin in the small intestine were exchanged for potassium in the colon. A study was therefore made of the transfer of ions between the mucosa of the colon and the cation exchange resin.

Observations on Cation-exchange Resin in the Colon

Three experiments were completed on patients taking a low-salt diet, without exchange resin by mouth. The colon was washed out with water. Two hours later approximately 5 g. of a 40-80 mesh sulphonic acid cation-exchange resin 100% in the sodium phase was introduced into the bowel through a high rectal tube. The foot of the bed was raised, and at intervals of 60-120 minutes samples of resin were removed via the tube or were obtained as the bowels were opened. In one group of experiments the sodium-phase resin was labelled with Na^{24} , and in another K^{42}Cl was injected intravenously two hours before the enema was given.

Results.—The composition of the exchange resin as put into the lower bowel and as removed 60-120 minutes later is given in Table I. Although samples of resin removed

TABLE I

Cation	In (mEq/g. of Resin)	Out (mEq/g. of Resin)	
		Mean	Range
Na	2.8-3.1	1.4	2.5-0.8
K	0	1.1	1.9-0.3
Ca	0	0.14	0.21-0.06
Mg	0	0.18	0.24-0.08

from the colon varied in composition the results were qualitatively similar. The exchange resin regularly lost sodium in the colon, and this was replaced by potassium and to a smaller extent by calcium and magnesium. The duration of these experiments was comparatively brief, and the results of these analyses do not represent the ultimate distribution of cations on the exchange resin. The net rates of exchange as measured by the radioactive isotopes were similar to those found by chemical analysis. It was impracticable to obtain frequent samples of resin from the colon, and for this reason it was not possible to compute the rates of ion exchange both to and from the resin. Data of this kind were therefore obtained by experiments on rats.

Effect of Laxatives

It had previously been observed that, of patients taking a low-salt diet and a cation-exchange resin, those with loose motions lost more sodium in the stools than did the subjects who were constipated (Spencer and Lloyd-Thomas, p. 597). From seven patients who were constipated on such a regime the stools were collected and analysed before, during, and after a period of 48 hours in which the motions were kept fluid by the administration of castor oil or cascara.

Results.—The effect of laxatives was to increase the mean faecal excretion of sodium from 21 to 63 mEq a day, and that of potassium from 69 to 103 mEq a day, as shown in Table II. It was apparent that the faecal excretion of sodium

TABLE II.—Daily Excretion of Cations in the Stools

	Total (mEq)		Bound to Resin (mEq/g.)		
	Na	K	Na	K	Na/K
Resin only	21 (13-37)	69 (58-106)	0.32	1.2	0.26
Resin and purge	63 (39-114)	103 (73-127)	0.68	0.93	0.73

had increased for three different reasons: first, the greater quantity of stool and resin passed; secondly, the electrolytes in the extra volume of stool water; and, lastly, because of the increment in sodium bound to each gramme of resin. The method of analysis permitted the separation of these components. When the bowels were freely open the mean

excretion of sodium bound to resin increased from 0.32 to 0.68 mEq/g. and the Na/K ratio rose from 0.26 to 0.73. It was thought that laxatives had modified the uptake of cations on the resin by changing the composition of the intestinal fluids and by accelerating the passage of exchange resin from the small intestine through the colon into the stools.

Experiments with Isolated Loops of Rat Intestine

Methods.—Loops of small intestine and colon of 250-g. rats were isolated by ligature, under ether anaesthesia. Special care was taken to preserve the blood supply. Small quantities of a 40-80 mesh carboxylic cation-exchange resin were introduced into the loops with the minimum amount of water, and the loops were then returned to the abdomen. At timed intervals (20-30 minutes) 2-cm. lengths of gut were excised and their content of resin recovered and analysed as described above. In one group of rats, Na^{24}Cl or K^{42}Cl (1 $\mu\text{c.}$ in 1 ml. of isotonic carrier) was injected subcutaneously two hours before the resin (100% hydrogen phase) was introduced into the gut. The data obtained permitted the calculation of the rates of transfer of sodium or potassium from the body fluids to the resin. In a second group, resin labelled with Na^{24} or K^{42} was introduced into the gut so that the rates of exchange in the direction resin to body fluid could be calculated. In a third group, resin which had equilibrated with the contents of the small intestine was transferred to the large intestine and samples of resin were removed at intervals and analysed as before. The analysis and interpretation of the data obtained follows the methods developed by Visscher *et al.* (1944) in their studies of cation transport across the intestinal mucosa. Details of these experiments will be reported elsewhere.

Results.—There is a continuous transfer of cations on and off the resin. The change in concentration of cations on the resin over a period of time is merely the net rate of transport, which is the algebraic sum of the rates of transport of cations on and off the resin. The net uptake of sodium and potassium by resin in the gut is shown in Fig. 2.

FIG. 2.—Net uptake of sodium potassium by a cation-exchange resin in the small and large intestine of the rat.

In the small intestine, 1 g. of resin took up 1.2-1.5 mEq of sodium and 0.3-0.45 mEq of potassium. When the resin in this state was transferred from the small to the large intestine it gradually lost sodium ions, but continued to take up potassium. The total Na^+ and K^+ bound to the resin fell, owing to the uptake of Mg^{++} and Ca^{++} . The ratio of sodium to potassium was 3-4:1 in the small intestine, 1:1 in the large intestine, and 0.4:1 in the faeces. The rates at which sodium and potassium were exchanged in the small intestine between the resin and its surrounding fluid after the attainment of a dynamic equilibrium were also determined. From these results it was calculated that all the sodium on the resin was turned over once every 60-75 minutes. With 5 g. of resin in the rat's small intestine, the turnover of sodium ions to and from the resin would

approximately equal the exchangeable body sodium every two hours. The turnover rate of potassium was one-half to one-third that of sodium.

Discussion

When a cation exchange resin is shaken up with an electrolyte solution in a simple container, such as a test-tube, an equilibrium distribution of ions between the resin and the solution is quickly reached. In the present experiments more than 90 minutes was required before a steady state was reached between the resin and the fluid in the rat's small intestine. The presence of resin in the gut introduces, in effect, a further electrolyte-containing compartment into the organism, the sodium and potassium of which require time to come into equilibrium with the exchangeable sodium and potassium of the body.

Even when the concentration of cations on the resin has reached the maximum for that section of the intestinal tract, there is a constant exchange of ions to and from the resin and the surrounding fluid. A series of dynamic equilibria are established between the cations on the exchange resin, those in the intestinal fluids, and eventually with those in the total exchangeable pool of cations in the body. In the rat the total exchange of sodium to and from the resin in two hours was found to be approximately equal to the entire sodium content of the body. The turnover rate for sodium was about three times greater than that for potassium. Exchange rates in the colon were slower and more variable than those in the small intestine.

However, the final concentration of cations on the exchange resin in the gut appears to depend only on the type of resin, the pH, and the concentration and physical properties of the different ions in the surrounding fluid. When an exchange resin was placed in solutions of the same pH and electrolyte concentration as the fluids of the small intestine and the colon, it took up cations in approximately the same proportions as those found on resin actually removed from these sections of the intestinal tract.

As the cation-exchange resin passes along the intestinal tract it undergoes a sequence of changes (Fig. 3). These net changes in the concentration of ions on the resin are the

resultant of the simultaneous movement of cations on and off the resin.

In the fasting stomach, at a pH of 2 or less, the resin remains largely in the hydrogen phase. If ingested in the ammonium and potassium forms some of these ions are exchanged for hydrogen ions. When there is a simultaneous ingestion of exchange resin and food, the net up-

In the small intestine there is a net uptake of sodium reaching up to 1.5 mEq/g. of resin in our experiments, and of potassium 0.3–0.5 mEq/g. of resin. Here the concentration of sodium in the intestinal fluid (86–134 mEq/l.) is much greater than that of potassium (6–17 mEq/l.), and this more than compensates for the smaller affinity of the resin for sodium as compared with potassium. If the ingested resin contains more potassium than 0.5 mEq/g. of resin the excess is exchanged for sodium. The concentration of electrolytes in the jejunal fluids is altered by ingested food, and this factor influences the net uptake of cations by the resin at this level of the intestinal tract. With a low-sodium, high-potassium diet, the resin takes up a preponderance of potassium ions in the jejunum, most of which is displaced by sodium lower down in the small intestine. Resin ingested in the ammonium phase continues to lose this ion.

By the time the resin has reached the proximal colon a net loss of sodium is already apparent, largely in exchange for potassium ions. This process continues as the resin passes along the colon to the rectum, the concentration of cations on the resin in the proximal colon being 0.9 mEq of sodium per g. of resin, and 0.8 mEq of potassium per g. of resin; and in the stools 0.4 mEq of sodium and 1.1 mEq of potassium per g. of resin. The concentration of electrolytes, expressed as mEq/l. of water of the gut contents, gradually changes along the course of the large intestine. In the caecum the values were similar to those in the small intestine—sodium 93–118 mEq/l., potassium 12–21 mEq/l. In the sigmoid colon and in the stool water, however, there was generally more potassium than sodium, the concentrations being sodium 6–38 mEq/l., potassium 14–44 mEq/l. Throughout the length of the gut the cations in the intestinal fluids compete for the free valencies in the resin. In the colon the net exchange of sodium ions bound to the resin for potassium and other ions merely results from the change in concentration and relative proportions of these ions in the fluids of the large bowel. It is possible that this exchange of sodium for potassium may begin in the distal part of the small intestine. When resin is ingested in the ammonium phase some 10–20% of the resin in the stools is still in this phase. The low-salt diet used in these studies was also comparatively low in calcium and magnesium, but resin in the stool contained up to 0.3 mEq/g. of resin of both these ions, the quantity actually bound to the resin varying with the pH of the stools when analysed.

When dietary sodium is low there is a reduction in the excretion of sodium bound to exchange resin in the stool (Dock and Frank, 1950; Greenman *et al.*, 1951; Martz *et al.*, 1952), and this decrease is most conspicuous in salt-depleted subjects (Emerson *et al.*, 1951). Berger and Steele (1952) have suggested, therefore, that the electrolyte content of the intestinal fluids is altered by salt depletion, in response to increased secretory activity of the adrenal cortex. The observation that injections of deoxycortone acetate decrease the faecal excretion of sodium bound to resin (Berger *et al.*, 1951) appears to support this concept. While it is true that McCance (1938) has reported change in the electrolyte content of the salivary and gastric juices during severe salt depletion, there does not appear to be any direct evidence of similar alterations in the composition of the fluids in the small and large intestines.

In the present studies the patients were maintained on a low-salt diet, but were not seriously depleted of sodium. Under these conditions, exchange resin removed from the small intestine was still predominantly bound to sodium. Salt restriction did not materially alter the sodium content of the fluid in the small intestine. In the same patients the excretion of sodium bound to resin in the stool was low. It would therefore seem that the effect of salt restriction was to make the colon more efficient at removing sodium from the resin. The reabsorption of sodium is a normal function of the colon, and the increased efficiency of this mechanism during salt restriction is comparable to that exhibited by the sweat glands and the kidneys.

FIG. 3.—Mean concentration of cations bound to an exchange resin during its passage along the human gastro-intestinal tract.

take of cations by the resin will vary greatly according to the electrolyte content of the diet and the pH of the stomach. The hydrogen-ion concentration is important for two reasons. First, the uptake of cations by carboxylic resins, and to a much smaller extent by sulphonic acid resins, is dependent on the pH (Nachod, 1949). Secondly, in the presence of phosphate ions the availability of calcium and magnesium ions for exchange is greatly increased in acid solutions. Under these conditions there is a considerable uptake of calcium and magnesium from the diet of an acid stomach (pH 3–6). Because of the great affinity of exchange resins for these ions, they are not subsequently displaced to any considerable extent by sodium or potassium ions.

By the use of laxatives it was possible to increase the faecal excretion of sodium during the ingestion of cation-exchange resins. However, a great increment in sodium excretion was obtained only when the stools were kept fluid. Vigorous treatment of this kind is not recommended, as, besides the discomfort, purgatives greatly augment the excretion of potassium in the stool water. During treatment with cation-exchange resins the aim should be to keep the motions loose but not actually fluid, and to supplement the dietary intake of potassium. Saline laxatives, the cations of which become bound to the resin, and liquid paraffin, which coats the resin with a water-repellent film, must of course be avoided.

Summary

The net uptake of cations by an exchange resin was determined at different levels of the intestinal tract in man. The rates of turnover of Na^{24} and K^{42} to and from the resin were also measured in the small and large intestines of the rat.

A series of dynamic equilibria are established between the cations on the exchange resin and those in the intestinal fluids. These transfers are continuous throughout the gut, but the rates of turnover and the net uptake of cations by the resin change as it passes onwards from the stomach to the rectum.

Cations throughout the body continually exchange with those on the resin by way of the intestinal fluids.

These concepts have been used to interpret the results obtained during the treatment of patients with cation-exchange resins.

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The Minister of Food, Major Gwilym Lloyd-George, M.P., has approved for publication a report presented to the Food Standards Committee by its Metallic Contamination Subcommittee on the amount of zinc that should be permitted in food. The report recommends that no exception need be taken to the presence of traces of zinc in foods in amounts not exceeding, in "beverages ready to drink," 5 parts per million (p.p.m.), and in other foods 50 p.p.m. This recommendation is subject to a few exceptions; thus a limit of 100 p.p.m. has already been prescribed for edible gelatin, and the subcommittee sees no objection to the sale of certain animal and vegetable products with a high natural zinc content—even when it exceeds 50 p.p.m. Attention is drawn in the report to the undesirability of using zinc and galvanized iron containers in the preparation or storage of foods. The subcommittee states that zinc, like copper, has a definite physiological function in the human organism. The normal daily intake of an adult is estimated at 12 mg. It considers that public health requirements would be met by observance of the limits proposed, and that, in the absence of any new developments, statutory effect need not be given to the limits recommended.

CARCINOMA COMPLICATED BY PROXIMAL MOTOR NEUROPATHY DUE TO VITAMIN-B DEFICIENCY

BY

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Though the number of cases of neuropathy associated with cancer is not so far very great, it is probable that many are overlooked, and that patients who might otherwise have lived useful lives for months or years suffer unnecessarily or come to an untimely end. The general practitioner must usually undertake the care of the patient with incurable malignant disease, and he is unlikely to be aware of this particular complication, still less that it responds well to the correct treatment if given promptly.

The Literature

Spillane (1947) reviewed the effects on the central nervous system of deficiencies of the various members of the vitamin-B group. Cases of neuropathy associated with carcinoma, including many cases of true peripheral neuropathy with sensory disturbances, are reviewed by Denny-Brown (1948) and by Lennox and Prichard (1950). The cases of true peripheral neuropathy are not dealt with here.

Five cases of neuropathy associated with carcinoma of the bronchus were reported by Lennox and Prichard. Two actually under their care (Cases 1 and 2) were typical of peripheral neuropathy with motor and sensory phenomena. The other three (Cases 3, 4, and 5) seem quite different, and may have been similar to the cases reported below from the Royal Cancer Hospital. The points of difference which stand out include:

Cases 1 and 2

1. Sensory symptoms early.
2. True peripheral weakness—for example, foot-drop.
3. Chronic course and absence of brain-stem lesions.

Cases 3, 4, and 5

1. Absent or minimal sensory phenomena, subjective and objective.
2. An early symptom, at any rate in Cases 3 and 5, was inability to sit up in bed; perusal of the clinical description leaves a very real doubt regarding the main sites of weakness. The evidence suggests that the proximal musculature bore the main brunt. In Case 4 the details given are insufficient to throw light on this aspect.
3. Palatal weakness, dysphagia, and, in Case 5, facial weakness were involved—that is, the brain-stem was rapidly and severely affected.

Heathfield and Aldren-Turner (1952) described a case of neuropathy associated with presumed carcinoma of the bronchus. In this case no sensory symptoms and few sensory signs were elicited, and the weakness seems to have involved the hips and knees as well as the ankles and, only slightly, the