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A CRITICAL ANALYSIS OF CATION-EXCHANGE THERAPY

BY

A. G. SPENCER, M.D., M.R.C.P.

AND

H. G. L. LLOYD-THOMAS, M.B., M.R.C.P.

(From the Medical Unit, University College Hospital Medical School, London)

It is now established that cation-exchange resins are sometimes an effective adjuvant to a low-salt diet in the treatment of oedema. The early hope that the use of ion-exchange resins would allow patients with cardiac oedema to take a more liberal diet and an increased intake of salt has not been realized (Greenman *et al.*, 1953). The main advantages now appear to be these: first, resin treatment may succeed when other methods have failed; secondly, by preventing the absorption of sodium and the reaccumulation of oedema fluid, the patient may be spared much discomfort, and the periodic use of mercurial diuretics becomes unnecessary.

It is often difficult to assess the contribution of ion-exchange resins to the successful results that have been reported. This is because a preliminary control period has not always been obtained, and because resin therapy has been used simultaneously with other forms of treatment, such as mercurial diuretics (Elkinton *et al.*, 1952), A.C.T.H. (Greenman *et al.*, 1951b), and abdominal paracentesis (Payne and Wilkinson, 1951). In addition, the published results show a great variation in the response of individual patients; in some a negative sodium balance was not obtained (Danowski *et al.*, 1951; Klingensmith and Elkinton, 1952), and it seems certain that these patients failed to benefit from ion-exchange therapy. Serious complications such as acidosis and potassium depletion are common to many reports (Dock and Frank, 1950; Greenman *et al.*, 1953) and were encountered in the present series. Although resins are now available in a palatable form, the large bulk that must be ingested, the relatively high cost, and the close chemical control that is necessary during treatment are practical reasons for restricting their use. Moreover, the response of many patients to rest in bed, a low-salt diet, digitalis, and mercurial diuretics is so good that no other treatment is needed.

It is clear that the selection and management of patients require considerable experience and care. Despite an abundance of biochemical data, there is little information to guide the practitioner in the safe and effective use of cation-exchange resins. The purpose of the present paper, therefore, is to present and analyse the results obtained over the past three years with special reference to the selection of patients, the methods by which dangerous complications can be avoided, and the most effective use of the resins now available.

Material and Methods

Observations were made on 39 patients with peripheral oedema due to cardiac (30) or renal (9) disease (Table II). The patients were not specially selected, and included those with all degrees of oedema from gross anasarca to minimal ankle-swelling; but many (32) had persistent chronic oedema which had failed to respond to intensive treatment by all the standard methods.

The patients were treated in bed on a constant regime, taking a low-salt diet with a restricted fluid intake of 40 oz. (1,140 ml.) a day. Six diets were analysed in duplicate, and the cation content is given in Table I.

TABLE I.—Daily Cation Content of the Low-salt Diet; Data Obtained by Analysis

	Mean	Range
Sodium ..	15 mEq	11–23 mEq
Potassium ..	48 "	41–65 "
Calcium ..	631 mg.	614–654 mg.
Magnesium ..	312 "	305–344 "
Iron ..	11 "	10–12.5 mg.

Metabolic balance studies for sodium and potassium were obtained on 12 patients during 42 three-day collection periods, and for calcium, magnesium, and iron on six patients. The diet and stools were homogenized and aliquots ashed at 550° C. in a muffle furnace. The methods of analysis were the standard techniques previously described from this laboratory (Spencer, 1950; Nabarro *et al.*, 1952); inorganic iron and calcium were determined by the methods described by Hawk *et al.* (1947). Frequent observations were made on the plasma electrolyte concentrations and on the patients' weights.

A sulphonated polystyrene cation-exchange resin was administered as a 3:1 mixture of the ammonium and potassium phases (katonium), except for four patients who were given hydrogen-phase resin ("zeo-karb 225 H") and four who received a mixed cation-anion exchanger 29% in the potassium phase ("carbo-resin"). The usual dose was 20 g. thrice daily suspended in a liquid vehicle, taken after meals. Treatment lasted from two to eight weeks, with an average of 3.6 weeks. A special watch was kept for clinical and chemical complications, and records were kept of the patients' complaints.

There can be no doubt about the successful treatment of oedema: there is a rapid loss of weight, a water diuresis, and the swelling is grossly diminished.

Our results have been classified on the following basis:

	Excellent Over 14 lb. (6.4 kg.) ++++	Moderate 14-7 lb. (6.4-3.2 kg.) ++	Failure 0-7 lb. (0-3.2 kg.) +→0
Loss in weight			
.. of oedema			
Excess urine volume over fluid intake (Total)	Over 7 litres	7-3 litres	<3 litres

Seven of the 39 patients had insufficient oedema to permit classification of their response in this way, and these are grouped in Table II as "not assessed." They are included in the series to give a true overall account of the patients and of the incidence of complications during treatment.

Whereas the effective treatment of oedema is obvious, the credit is easily allotted to one particular form of therapy when it should be given to a combination of several, or, more correctly, recognized as a spontaneous improvement independent of any. To reduce this error, all patients were observed during a preliminary period of at least three weeks' (average five weeks) treatment by rest in bed, a low-salt diet, and fluid restriction; digitalis and mercurial diuretics were given when indicated. Except for the diuretics, this basal treatment was continued during the administration of the cation-exchange resins, and the results obtained are not considered as an unaided response to resin therapy.

Results

The clinical results obtained in 39 patients during the administration of ion-exchange resins are summarized in Table II. In 34% of the patients there was an excellent response, with clearing of massive oedema. Considerable

TABLE II.—Clinical Response of 39 Patients to Ion-exchange Resins, Classified According to the Standards Given in the Text

	Total	Clinical Response			
		Excellent	Moderate	Failure	Not Assessed
Heart disease:					
Rheumatic ..	8	3	3	2	0
Ischaemic ..	19	4	3	5	7
Cor pulmonale	3	1	1	1	0
Renal disease:					
Type II nephritis	7	4	0	3	0
Chronic ..	2	1	1	0	0
Total ..	39	13	8	11	7

improvement was obtained in a further 21%, with loss of oedema and weight up to 14 lb. (6.4 kg.); but in 45% no definite benefit resulted. If the seven patients with minimal oedema are excluded, an excellent response or considerable improvement was obtained in 65%. The resins were most effective in type II nephritis in the absence of uraemia, and in chronic rheumatic heart disease without cardiac cirrhosis. Poor results were obtained in patients with very chronic or recurrent congestive cardiac failure, whether due to advanced disease of the coronary arteries or to rheumatic heart disease; in those with renal failure; and in oedematous patients with a plasma sodium below 130 mEq/l. after long-continued treatment by salt depletion. Three seriously ill patients died during treatment—the first from a large pulmonary embolus, the second and third from advanced coronary artery disease.

Patients' Complaints

The frequency and type of complaints induced by the ingestion of resins were similar to those reported by Klingensmith and Elkinton (1952), and are summarized in Table III. In 67% there was discomfort, mainly related to the gastro-intestinal tract, and in 11% this was severe enough to cause the treatment to be abandoned. In 10% the complaints were moderately severe but were relieved by adjust-

TABLE III.—Incidence of Complaints During Cation-exchange Therapy

Incidence of Complaints		Severity	
Anorexia ..	12	Weakness ..	7
Constipation ..	11	Paraesthesia ..	4
Nausea ..	9	Sore mouth ..	4
Vomiting ..	4	Haematemesis ..	1
Abdominal pain ..	6	Alopecia ..	1
Diarrhoea ..	4		

Nil ..	33%
Mild ..	46%
Moderate ..	10%
Severe ..	11%

ments to the regime; while in 46% symptoms were slight. Although only 33% of these patients were entirely free from symptoms, severe gastro-intestinal complaints such as stomatitis and vomiting were confined to four subjects who were given the 100% hydrogen-phase resin in the early stages of this investigation. Resin preparations which were more palatable soon became available; these could be taken by most patients over periods of several weeks. Despite these improvements, patients still objected to the large bulk of resin that was required for effective treatment.

Biochemical disorders frequently developed during treatment with cation-exchange resins, but were not often serious. A characteristic metabolic response to resin therapy is illustrated in Fig. 1, which summarizes the data obtained in the following patient.

Case 4.—A woman aged 44 had type II nephritis, with gross anasarca, ascites, and pleural effusions. B.P. 110/70; serum albumin, 1.8 g./100 ml.; plasma cholesterol, 710 mg./100 ml.; blood urea, 24 mg./100 ml., with a maximum urea clearance of 83% of normal; albuminuria 16 parts per 1,000 (1.6 g./100 ml.). There was no improvement during three weeks' treatment with rest in bed and a low-salt diet containing 15 mEq of sodium.

The ingestion of 60 g. a day of a cation-exchange resin was followed by complete relief of the oedema in four weeks, a weight loss of 16 kg. and a negative sodium balance totalling 1,860 mEq.

The bowels were opened twice daily by a laxative. The faecal excretion of sodium was the greatest obtained in this series of patients, but an increased renal loss of water and salt accounted for 67% of the negative sodium balance. The stool potassium increased from 8 to 96 mEq a day, and the patient developed a negative potassium balance, hypokalaemia, and a compensated hyperchloraemic acidosis. These were corrected by supplements of potassium citrate, 2 g. three times daily. As the oedema disappeared the albuminuria decreased from 16 parts to 1 part per 1,000, the serum albumin gradually rose from 1.8 to 4.8 g./100 ml., and the plasma cholesterol fell from 710 to 265 mg. per 100 ml. One year later the patient was free of oedema and in good health, with normal renal function and normal urine.

FIG. 1.—Metabolic balance chart of Case 4, type II nephritis, during treatment with ion-exchange resin. The black columns represent the stool electrolytes, while the renal excretion is unshaded. The intake is at the level of the interrupted lines, and the output is plotted upwards from zero. A negative balance is shown when the columns extend above the interrupted lines.

Sodium Depletion

The object of resin therapy was, of course, to deplete the body of excess sodium contained in the oedema fluid, and this was achieved in 8 out of 12 patients on whom balance studies were obtained (Table IV). The mean nega-

TABLE IV.—*Sodium Balances of 12 Patients Receiving 60 g. of a Cation-exchange Resin and a Sodium Intake of 15 mEq a Day*

Case No.	Mean Daily Balance of Sodium			Total Balance			
	Urine Na (mEq)	Stools Na (mEq)	Balance mEq	Days	Sodium (mEq)	Water (Litres)	Weight (Kg.)
1	34	17	-36	18	-648	-10	-12
2	4	22	-11	14	-154	0	-1
3	36	21	-42	23	-966	-6	-7
4	18	64	-67	28	-1,876	-14	-16
5	0	12	+2	6	+12	0	0
6	37	41	-63	12	-766	-4	-6
7	2	21	-8	6	-48	0	-3
8	18	37	-40	10	-400	-1	-2
9	0	12	-3	6	-18	0	0
10	38	15	-39	28	-1,092	-9	-11
11	22	52	-57	6	-342	-3	-5
12	34	18	-37	35	-1,295	-9	-12

tive balance of sodium in these eight subjects was 48 mEq a day, and the total sodium depletion was very great in patients relieved of gross oedema. These studies demonstrate that the action of cation-exchange resins is not confined to the removal of dietary sodium as suggested by Dock and Frank (1950) and Danowski *et al.* (1951); but also show that they extract sodium from the body fluids, thus confirming the results of Duncan (1953). The faecal excretion of sodium varied greatly in different patients, and

often declined during prolonged treatment, as it did in the studies of Cobbe *et al.* (1949), Emerson *et al.* (1951), and Barker and Mackay (1951).

A major factor, however, in the relief of oedema during resin therapy was an increased renal excretion of water and salt as noted by Greenman *et al.* (1951a). Thus the increment of sodium excretion generally had two components, an increased faecal excretion accounting for 42%, and that in the urine for the remaining 58% (Figs. 2 and 3).

The salt-depletion syndrome characterized by

FIG. 2.—Mean daily excretion of cations in the urine of 12 oedematous patients before and during the administration of a cation-exchange resin and a low-salt diet.

FIG. 3.—Mean daily excretion of cations in the stools of 12 oedematous patients before and during the administration of a cation-exchange resin and a low-salt diet.

weakness, anorexia, nausea, muscular cramps, a fall in blood pressure, oliguria, and uraemia, together with a low plasma sodium, was not observed in any of our patients. In nine a complaint of anorexia and nausea was not associated with any other indication of salt depletion, and possibly resulted from the local action of the resin on the gastro-intestinal

tract. Weakness was observed in seven subjects, but this was accompanied by a low plasma potassium. A normal blood urea and a plasma sodium over 130 mEq/l. is strong evidence against the existence of a serious degree of salt depletion.

The plasma sodium concentration did not fall significantly in any of the patients (Fig. 4), the mean sodium concentration remaining unchanged at 137-138 mEq/l. (81 observations). These results are similar to those reported by Kraus (1950) and by Klingensmith and Elkinton (1952); but a fall in plasma sodium during resin therapy was observed by Greenman *et al.* (1953) and Weston

et al. (1953). The initial plasma sodium concentration was usually lower in oedematous patients (mean, 137 mEq/l.) than in normal subjects (mean, 142 mEq/l.). In six it was below 130 mEq/l., but during administration of the ion-exchange resin it did not fall any lower. The blood urea did not rise during resin treatment except in those patients with pre-existing renal failure.

Potassium Depletion

Significant potassium depletion developed in 19 out of 39 patients, as shown by the incidence of muscular weakness (7), paraesthesiae (4), electrocardiographic changes (4), digitalis sensitization (4). The plasma potassium concentration fell below 4 mEq/l. in 26 out of 83 observations. Kraus (1950) and Greenman *et al.* (1953) experienced a comparable incidence. Potassium depletion results from a gross increase in the faecal excretion of potassium, mean 70 mEq a day (Fig. 3). The renal excretion of this ion usually decreased during resin therapy, except when potassium supplements were given (Fig. 2). The deficiency was closely related to the total intake of potassium, as it was less commonly found in patients taking a resin mixture 25% in the potassium phase, and was reduced still further by supplements of potassium citrate, 2 g. three times daily (Table V). Kling-

TABLE V.—*Effect of Potassium Intake on the Plasma Concentration and Balance of Potassium of Patients Taking 60 g. a Day of a Cation-exchange Resin*

Total Potassium Intake (mEq/day)	Potassium Balance (mEq/week)	Plasma Potassium After 2 Weeks
41-65 (diet + 100% hydrogen-phase resin)	-270	2.1-2.9 mEq/l.
70-98 (diet + 25% potassium-phase resin)	-80	3.2-5.1 "
90-108 (diet + 25% potassium-phase resin + 20 m.mols potassium citrate)	+20	4.3-7.5 "

ensmith and Elkinton (1952) avoided potassium depletion by administering resin 30% in the potassium phase, while Weston *et al.* (1953) recommended supplements of potassium salts for this purpose. Potassium depletion was not always avoided by these means, and occurred whenever our patients failed, through lack of appetite, to eat all their diet.

Potassium Retention

Potassium retention occurred in two oedematous patients with impaired renal function during treatment with 25% potassium-phase resin, the plasma concentration rising to 7.5 and 7.8 mEq/l. This has also been described by Peel and Semple (1953).

FIG. 4.—Plasma concentration of sodium and chloride ions before and during cation-exchange therapy. Means and ranges of 141 determinations on 28 patients. The graph is drawn through the means, while the vertical lines represent the ranges.

Depletion of Calcium, Magnesium, and Iron

There was no clinical evidence of depletion of calcium, although tetany (Dock and Frank, 1950; Martz *et al.*, 1952), and a low serum calcium (Greenblatt and Gilwood, 1948; Greenman *et al.*, 1953) have been reported during prolonged treatment with ion-exchange resins. The mean faecal calcium excretion increased from 405 to 518 mg. a day, but renal losses decreased from an average of 251 to 106 mg. a day (Figs. 2 and 3), and a small negative balance was found in only two patients. The mean faecal excretion of magnesium rose from 215 to 311 mg. a day and renal losses fell from 152 to 64 mg. a day, producing a mean negative balance of 46 mg. a day. No changes were observed in the serum calcium, but in five subjects the plasma magnesium was low, the mean being 2.4 mg./100 ml. (normal 4 mg./100 ml.). The faecal excretion of iron was not altered by resin therapy, and the patients remained in balance. Apart from the experiments of McChesney *et al.* (1951) and McChesney (1952), little is known about the effects of resin therapy on the metabolism of magnesium and iron.

Acidosis

It was unusual for clinical signs of acidosis to appear during treatment with cation-exchange resins. The plasma chloride usually rose, the mean increasing from 98 to 105 mEq/l. (Fig. 4). This hyperchloraemia was associated with a decrease in the plasma bicarbonate, the mean falling from 25 to 16 mEq/l. (Fig. 5). These changes were more apparent when a hydrogen-cycle resin was used. Similar observations were made by Elkinton *et al.* (1952).

FIG. 5.—Plasma concentrations of potassium and bicarbonate ions before and during cation-exchange therapy. Means and ranges of 146 determinations on 28 patients. The graphs are drawn through the means while the vertical lines represent the ranges. A=Patients taking 60 g. of a 3:1 NH_4 :K-phase resin and a dietary intake of 68 mEq K. B=Patients taking 60 g. of a 3:1 NH_4 :K-phase resin and a dietary intake of 48 mEq K. C=Patients taking 60 g. of a 100% H-phase resin and a dietary intake of 48 mEq K.

deficient in early renal failure, and six patients developed clinical signs of acidosis, with the plasma chloride rising to 115 mEq/l. and the bicarbonate falling to 8 mEq/l. Acidosis was less apparent in four patients with renal disease who were treated with a mixed anion-cation exchanger, the mean plasma chloride being 106 mEq/l., and the bicarbonate 18 mEq/l.

Renal Failure

There was no evidence that renal failure ever resulted from resin therapy, but uraemia, acidosis, and electrolyte disorders were usually increased by this treatment. Serial determinations of the blood urea were made in 21 patients,

and in 15 these were normal throughout. Six subjects had a raised blood urea before treatment; in one of these the blood urea fell, but in the other five it increased rapidly, and treatment by exchange resins was abandoned on this account.

Factors Relating to the Effectiveness of Exchange Resins

The efficiency with which cation-exchange resins increase the loss of sodium in the stools when the diet is constant appears to be related to the intestinal motility, to the body sodium content, and to the total intake of potassium in relation to the dose of resin.

Intestinal Motility.—On the same intake of sodium and resin the faecal excretion of sodium varied greatly from one patient to another (12 to 64 mEq a day, Table IV), but when measured over a period of several days was relatively constant for the same individual. In only 4 of 12 patients taking resins did the stool sodium (mean, 48 mEq a day) clearly exceed the intake, and these had loose motions; whereas in eight constipated patients the mean daily faecal excretion of sodium was 17 mEq a day. Laxatives consistently increased the loss of sodium in the stool, in part because of the extra quantity of resin passed and of the electrolytes contained in the larger volume of stool water, but largely due to the increment in sodium bound per gramme of resin. Potassium excretion also rose, but to a smaller degree, and the ratio of Na/K ions on the resin was greatly increased whenever the bowel motility was rapid. The stool sodium of four subjects taking resins was constantly very low, and, although this was increased by laxatives, the absolute loss of sodium was still comparatively small. The significance of these observations in relation to the dynamics of cation-exchange resins in the intestines is considered in detail by Spencer, Ross, and Lloyd-Thomas (p. 603 of this issue).

Total Body Sodium.—During prolonged treatment the mean faecal excretion of sodium declined, from 38 mEq a day during the first week to 22 mEq a day after six to eight weeks, but at the same time the oedema became less extensive. Stool sodium was also greater in the first week of treatment in grossly oedematous patients (mean 46 mEq a day) than in those with slight oedema (mean 27 mEq a day). However, in four patients with extensive oedema associated with a plasma sodium between 126 and 130 mEq/l. the faecal excretion of sodium in response to resins was only 14 mEq a day. The ion-exchange resins are therefore more efficient when the total body sodium is increased, except when the plasma sodium concentration is low.

Dietary Potassium.—The faecal excretion of sodium was decreased by increasing the dietary intake of potassium. With a combined potassium intake in the diet and on the resin of 88 mEq a day the mean excretion of sodium in a group of eight patients was 32 mEq a day. When extra potassium was given to a total of 108 mEq a day, the mean stool sodium declined to 24 mEq a day.

Discussion

The value of ion-exchange resins in the treatment of oedema is seriously limited by their small exchange capacity, and even more by the complete lack of specificity for the sodium ion. For example, the resin mainly used in the present study has a maximum capacity of only 3.1 mEq/g. and combines with three to four times as much potassium as sodium when in equilibrium with solutions containing equal proportions of these ions. Whereas resins are available with an *in vitro* capacity of up to 10 mEq/g. (Duncan, 1953), this has not been achieved at the hydron concentration of the intestines. Moreover, all these resins exhibit a descending order of affinities for cations, $\text{Ca}^{++} > \text{Mg}^{++} > \text{K}^{+} > \text{Na}^{+} > \text{NH}_4^{+} > \text{H}^{+}$ (Nachod, 1949).

Considering the high concentration of sodium in the small-intestinal juices, the failure of cation-exchange resins to extract large amounts of this ion from the alimentary

tract of all subjects ingesting the resin has occasioned surprise (Dock and Frank, 1950). This has led to statements that ingested exchange resins extract sodium only from the diet and the upper small intestine (Hegsted *et al.*, 1951), or that increased secretory activity of the adrenal cortex in response to sodium depletion grossly alters the sodium content of the alimentary secretions (Berger *et al.*, 1951; Berger and Steele, 1952). Such conceptions of the action of exchange resins in the body are at variance with their known physical properties. Moreover, studies from this department, using the radioactive tracers Na^{24} and K^{42} have demonstrated that cation-exchange resins establish a dynamic equilibrium with the intestinal contents throughout the alimentary tract. There is a continuous interchange of ions to and from the resin and the body pool of sodium and potassium, with a rate of turnover at least equal to the total body content of these electrolytes every 24 hours. Large quantities of sodium are taken up by the resin in the small intestine even when there is only a small excretion of this ion bound to the resin in the stools. Most of the sodium taken up in the small intestine is exchanged for potassium in the colon (Spencer, Ross, and Lloyd-Thomas, p. 603).

From these observations, it appears that the efficiency of ion-exchange resins in the treatment of oedema could be increased in at least three different ways: first, by avoiding constipation; secondly, by developing resins which have a high exchange capacity and a special affinity for sodium; thirdly, by influencing cation exchange across the mucosa of the small intestine and colon, as by the use of specific enzyme inhibitors.

In their present stage of development cation-exchange resins cannot be recommended for general use in the treatment of oedema. Most oedematous patients respond well to treatment by rest in bed, a low-salt diet, digitalis, and mercurial diuretics. These measures are generally so simple, effective, and safe that cation-exchange therapy is not likely to replace them. Some patients, however, remain oedematous despite vigorous treatment by these standard methods, and in others mercurial diuretics are contraindicated. It is in these patients that resin therapy finds its most useful application; but not all of these benefit, and in others serious complications may occur. An attempt has been made to define these two groups from an analysis of the results obtained in the present series and from those previously published. It now seems possible to select patients and manage their treatment with ion-exchange resins so that the majority become free of oedema without the risk of grave metabolic disorders.

Indications

1. *Cardiovascular Disease*.—In the absence of contraindications, treatment by ion-exchange resins is advised: (a) in persistent congestive cardiac failure of all types when pitting oedema remains after two to three weeks' treatment by standard methods; (b) when mercurial diuretics or digitalis are contraindicated because of sensitivity, toxicity, or failure to respond; and (c) during the convalescence from heart failure to prevent the recurrence of oedema. A satisfactory response is less often obtained in the presence of extensive disease of the coronary arteries, chronic congestive heart failure with cirrhosis of the liver and ascites, and whenever intensive salt depletion by other means has failed to relieve oedema. Two points merit further consideration. When the routine treatment of oedema has failed, resin therapy should not be delayed. Prolonged immobilization in bed leads to a steady deterioration, and greatly increases the risk of venous thrombosis and pulmonary embolism. Although the relief of oedema is highly desirable, it does not necessarily indicate any considerable improvement in cardiac function. In fact, treatment by resins or by other methods of salt depletion often removes many of the cardinal signs of heart failure.

Hypertensive Disease.—The use of cation-exchange resins together with a low-salt diet has been advocated as a more practical alternative to the rice diet in the treatment of

hypertension (Page, 1951; Gill and Duncan, 1952). However, six of our patients with a high blood pressure were treated in this way, and in only one was there an appreciable fall of blood pressure. The most useful application of resin therapy in hypertensive disease therefore seems to be in cardiac failure. Little information is available concerning the value of exchange resins in patients with cardiac asthma or with hypertensive encephalopathy.

Renal Disease.—An excellent response may be obtained in type II nephritis and in early diabetic nephrosclerosis, provided that the blood urea is not raised. Patients with chronic nephritis and oedema commonly have advanced renal failure and are made worse by resin therapy. Sodium-phase resins have been successfully used in the management of hyperkalaemia occurring in anuria (Merrill *et al.*, 1950; Bull, 1952).

Contraindications

Gastro-intestinal Disorders.—A poor appetite, nausea, and dyspepsia interfere with the continued ingestion of the resin or, by causing gross fluctuations in the dietary intake, precipitate potassium depletion. Anorexia and nausea are among the symptoms of sodium depletion, and are often indications for an estimation of the plasma sodium and the blood urea.

Renal Failure.—The absence of an effective renal compensation for electrolyte disorders should generally be an absolute contraindication to treatment by ion-exchange resins. Metabolic complications such as severe hyperchloraemic acidosis, potassium retention or depletion, and a rapid elevation of the blood urea are common; whereas relief from oedema is seldom achieved. The ammonium-phase resins contribute significantly to the nitrogen intake, and the usual dose is equivalent to the ingestion of 5 g. of urea a day. This extra load on the kidney would, if not excreted, raise the blood urea by 100 mg. per 100 ml. in ten days.

Advanced Liver Disease.—Ammonium phase resins may precipitate coma from ammonia intoxication in patients with advanced liver disease (Phillips *et al.*, 1952; Gabuzda *et al.*, 1952). Since effective sodium depletion can be achieved only by resins in the ammonium or hydrogen phases, and as the latter are unpalatable and likely to cause oesophageal erosions, resin treatment should not be used when liver function is severely impaired. Some excellent responses have been reported, however, in patients with cirrhosis of the liver (Gabuzda *et al.*, 1952).

Cation Depletion.—If in patients with heart failure the plasma sodium is consistently below 130 mEq/l., the daily urine volume is less than 500 ml., or the blood urea is over 60 mg./100 ml., treatment with cation-exchange resins is contraindicated. Uncorrected potassium depletion should be an absolute bar to cation-exchange therapy. This most commonly results from an inadequate intake of food associated with disease or operations on the gastro-intestinal tract, diarrhoea, and the previous use of exchange resins.

Management of Cation-exchange Treatment

The principles of management are these: to use exchange resins as an adjuvant to salt restriction, with digitalis, mercurial diuretics, and rest in bed when necessary; and to avoid complications by the exclusion of unsuitable patients, close supervision of the potassium intake, and the early detection of biochemical disorders.

Chemical Control.—Before treatment is begun it is advisable to measure the blood urea and the plasma concentration of sodium, potassium, and bicarbonate ions. The plasma potassium should be measured at intervals of one week. The treatment of patients with renal failure is not recommended, but, should there be doubt about the renal function, resin therapy may be tried, provided that weekly estimations of the blood urea, plasma bicarbonate, and potassium concentrations are available. It is helpful to keep a record of the weight, degree of oedema, urine volume, and bowel action.

Diet.—There is abundant evidence that the ingestion of exchange resins allows little increase in the intake of sodium (Greenman *et al.*, 1951a; Greenman *et al.*, 1953), and at first this should not exceed 20 mEq a day (1 g. salt). To avoid potassium depletion the intake needs to be maintained at 75 mEq (3 g.) potassium a day, in addition to that on the resin. The low-salt diet may not contain this amount of potassium, and the addition of fresh fruit will then form an acceptable supplement of this ion. Since a constant and relatively high intake of potassium is the chief safeguard against potassium depletion, close supervision of the patients' meals is required. Any failure to eat the diet should be recorded by the nurse and reported to the physician in charge. The addition of 1 pint (570 ml.) of milk a day makes the diet more palatable, and helps to prevent depletion of calcium and magnesium during prolonged therapy. Although exchange resins absorb thiamine (Nachod, 1949; McChesney and McAuliff, 1950), no evidence of vitamin deficiency has been observed during treatment (Greenman *et al.*, 1953). Nevertheless it may be advisable to provide a compound vitamin supplement. In the treatment of type II nephritis the introduction of up to 150 g. of protein into the diet is made more effective by the administration of exchange resins, which take up the increment in sodium.

Selection and Administration of the Resin.—Of the available preparations those containing a 3 : 1 mixture of the ammonium and potassium phases of a sulphonic or carboxylic cation-exchange resin are most generally useful. Ammonium-phase resins are contraindicated in advanced liver disease (Phillips *et al.*, 1952). The resins now in common use in this country have an effective combining capacity of about 3 mEq/g., and in adults the effective dose is 45–75 g. a day. These preparations are pleasantly flavoured, making them easy to take as a suspension in water or in fruit juices. It is immaterial whether the resins are given before or after meals (Martz *et al.*, 1952). The intermittent use of resins has been advocated by Weston *et al.* (1953). This reduces the risk of potassium depletion, the resin being given on five days a week with intervals of two days, in which potassium citrate, 2 g. three times a day, is provided in a simple mixture. There may be little response in the first ten days of treatment, but some of these patients rapidly improve thereafter. Resin therapy should therefore not be abandoned for this reason in less than two to three weeks.

Domiciliary Treatment.—In selected patients, treatment with ion-exchange resins and a modified low-salt diet (2 g. salt) has been continued at home for many months. This has successfully prevented the reaccumulation of oedema, and in this way has reduced the frequency of readmissions to hospital. These patients attend the follow-up clinic at intervals of two to four weeks for clinical supervision and estimation of the plasma electrolytes and the blood urea. Voyles and Orgain (1951) and Aaron and Weston (1952) have reported their experience of long-continued resin therapy.

Care of the Bowels.—Many patients have become constipated during the administration of exchange resins, and this may give rise to abdominal swelling and discomfort (Arnold, 1951). In the present study it has been demonstrated that the efficiency with which resins remove sodium from the gastro-intestinal tract was decreased by constipation and increased by the use of aperients. For this reason it is recommended that the bowels should be opened once or twice a day, obtaining soft stools by any laxative which suits the patient. Salts should not be used for this purpose, and diarrhoea must be avoided.

Administration of Digitalis.—An increased incidence of digitalis toxicity has been reported during treatment with cation-exchange resins (Kraus, 1950; Weston *et al.*, 1953). Gross disturbances of this kind were seen in 3 out of 28 patients in this series who were taking maintenance doses (0.25 to 0.75 mg. a day) of digoxin (Fig. 6). These occurred when the plasma potassium was reduced, and were relieved by the administration of potassium citrate. Special care

FIG. 6.—Digitalis toxicity associated with potassium depletion during the course of cation-exchange therapy. (a) Multiple ventricular extrasystoles. E.C.G. Lead I (rate 150 per minute). Plasma potassium, 3.6 mEq/l. (b) Auriculo-ventricular dissociation. E.C.G. Lead III (ventricular rate 79, auricular rate 130 per minute). Plasma potassium, 4.1 mEq/l.

should therefore be taken to avoid potassium depletion in patients taking both digitalis and ion-exchange resins. The maintenance dose of digitalis may be halved when the resin is begun, and increased later as indicated. The relation between potassium metabolism and the action of digitalis on the heart has been reviewed by Enselberg *et al.* (1950) and Lown *et al.* (1951).

Mercurial Diuretics.—Martz *et al.* (1952) and Elkinton *et al.* (1952) have reported that the efficiency of mercurial diuretics was increased during the administration of cation-exchange resins, and our recent experience confirms this observation.

Paracentesis.—When patients lose their oedema, effusions into the pleural and peritoneal cavities commonly persist. These are best removed by paracentesis in the early days of resin treatment.

Summary

Cation-exchange resins were administered to 39 patients with chronic oedema resulting from cardiac or renal disease.

A satisfactory response was obtained in 65% of those with gross oedema. Minor complaints induced by resin therapy occurred in 67%, but serious chemical disorders were uncommon.

Metabolic balance data were obtained in 12 patients, and the results are discussed and analysed in relation to the incidence of biochemical complications and to the clinical effectiveness of cation-exchange therapy.

Recommendations are made on the use of cation-exchange resins, with particular reference to the selection and management of patients and the methods by which dangerous complications can be avoided.

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CATION EXCHANGE IN THE GASTRO-INTESTINAL TRACT

BY

A. G. SPENCER, M.D., M.R.C.P.

E. J. ROSS, Ph.D., M.B.

AND

H. G. L. LLOYD-THOMAS, M.B., M.R.C.P.

(From the Medical Unit, University College Hospital Medical School, London, W.C.1)

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.