1952

Use of cation exchange resins in edematous states

William Clinton Kenner
University of Nebraska Medical Center

THE USE OF CATION EXCHANGE RESINS IN EDEMATOUS STATES

William Clinton Kenner III

Submitted in Partial Fulfillment for the Degree of Doctor of Medicine
College of Medicine, University of Nebraska
December 11, 1951
Omaha, Nebraska

CONTENTS

INTRODUCTION

The value of sodium deprivation in the control of edema has long been recognized by the medical profession. Also recognized in conjunction with this thearapy is the difficulty encountered by the patients in continuing the low sodium diet over long periods of time.

Several reasons account for this difficulty. Probably formost is the preparation of appetizing and nutritious menus for extended periods of time with restricted use of salt and salt containing foods. It is difficult, even in the hospital diet kitchen, to attain a precise regulation of dietary salt, while in the home salt intake may mount very rapidly unless vigorous attempts are made to stay within dietary limits. Some cases may not be controlled even by strict dietary curtailments of salt intake and must be aided by the mercurials and other diuretics.

Whichever the case may be, the cation exchange resins offer a valuable aid in easing the rigors of therapy in the control of edema. In the less severe cases they may allow a more liberal salt intake and thus increase the palatability of the diet in addition to lessening the difficulty in selection of foods and preparation of the daily menu. In more severe cases they may aid in more extensive sodium depletion than that attained by the previous low sodium diet and

mercurial diuretics, and in many cases may preclude the need of the mercurials altogether.

Another advantage offered by the cation exchange resins is the slow but continuous sodium depletion which they effect in contrast to the rapid, short acting mercurials which may result in an acute electrolyte imbalance.

It is the purpose of this theses to present an evaluation of the efficiency of cation exchange resins in the treatment of edematous states. Special attention will be paid to the type of resin and the hazards attendant its use.

HISTORY

Ion exchange substances have been used for centuries, but not until recent years have their physico-chemical properties been partially understood.

One of the first documented reports, dated 1850, concerned a substance called "terra sigillata" or "sealed earth" (1). In this report eight dogs were given various poisons, of the eight, four were given "terra sigillata" with the poison and survived, while the others died. Another account written in 1851 describes a successful experiment in which a condemned criminal was given the "earth" immediately following a lethal dose of mercury sublimate (1). In 1914 it was found that the composition of "terra sigillata" consisted of oxides of calcium and aluminum with a large proportion of silicates (1). However, at this time the properties of the substance were unexplained. In the light of present knowledge the properties of "terra sigillata" in these experiments may be explained on the physico-chemical grounds of an ion exchange substance.

Ion exchangers act by accepting one ion from a solution in exchange for another. Many naturally occurring exchange substances have been used in industrial processes for many years. As far back as 1896 they were used in the refining of sugar. Advancements over the naturally

occurring exchangers were made with the introduction of the "zeolites", a combination of sodium aluminate and sodium silicate, and synthetic organic exchangers, composed of sulfonated coals (2, 3, 4, 5, 6). The first synthetic ion exchange resins were produced in 1934 by Adams and Holmes (7). There resins were a synthetic phenol-formaldehyde resin with cation exchange properties and prepared from aromatic amines and formaldehyde which had anion exchange properties.

In 1945 the use of anion exchange resins were introduced in the medical treatment of peptic ulcer (8, 9, 10, 11, 12, 13, 14). These resins lowered gastric acidity either by removal of the acid radicals, expecially chloried, or of the whole acid molecule, a point which has not yet been determined.

A year later, in 1946, Dock showed that cation exchange resins could be administered to dogs and rats in massive oral doses with a significant increase of fecal sodium excretion without toxic effects (15). These findings prompted Dock to suggest the possible efficacy of these resins as an adjunct in the treatment of edematous states.

CHEMICAL COMPOSITION AND MODE OF ACTION

Cation exchange resins are completely insoluble synthetic organic acids. The carboxylic exchanger is a phenol-formaldehyde polymer of huge molecular weight, a product of turpentines (16). The resin exists as a sort of homogenous gel, over the surface of which are arranged many carboxylic acid radicals which serve as the sole ion active groups. This configuration enables the cations to be bound remotely to the molecular skeleton and thus available for exchange (17). The size of the molecule also gives it adsorptive properties. The sulfonic exchanger differs from the carboxylic form in that sulfonic groups take the place of the carboxylic.

The sulfonic resin is a strong organic acid. Its cation binding power is fully activated at all pHs above three. The carboxylic resin is a weak organic acid. It first begins to bind cations at a pH of five and increases in efficiency until its maximum efficiency is reached at a pH of eight.

The affinity of the resin for various cations is a function of the cation's molecular size, magnitude of charge, and concentration in solution (18). Thus, the resins would take up calcium and magnesium ions in preference to sodium or potassium if these ions were in equal concentration. However, in the gut calcium and magnesium are present in very small amounts while potassium and particularly sodium are found in high con-

centration. In view of this fact, one can assume that only small amounts of calcium and magnesium will be lost in the feces.

The main objective in the treatment of edema is control of sodium intake and output. In this respect the cation exchange resins theoretically appear to be of great value.

The mode of action of an ammonium carboxylic exchanger may be diagramatically represented as in Fig.I.

$$NH_4R + HCl \overset{pH<6}{\rightleftharpoons} NH_4Cl + HR$$

$$HR + NaCl \overset{pH>6}{\rightleftharpoons} NaR\downarrow + HCl$$
(Feces)

Fig.I

Ideally, the ammonium ion is exchanged for a hydrogen ion in the acid content of the stomach and this is then exchanged for sodium in the more alkaline portion of the gut and excreted in the feces. However, potassium, calsium, magnesium and other cations are also present in the gut and as stated before, are bound to the exchanger in proportion to their molecular size, magnitude of charge and concentration.

Most commercial cation exchange resins used in medicine now include a potassium form resin in conjunction with the hydrogen or ammonium carboxylic resin. The average binding capacity is 5 meq. of sodium per gram of resin.

CLINICAL INVESTIGATIONS

Cation exchange resins have been used in a great many edematous conditions. Many forms of the resins have been used in these conditions and it is the purpose here to present a summary of clinical findings showing the efficacy of these various forms. The most extensive work done thus far has been with three main groups of patients; those with edema due to congestive heart failure, those with cirrhosis of the liver, and those exhibiting the nephrotic syndrome. Other studies have been done with patients exhibiting other edematous states but since little information concerning these studies is as yet available they will not be included here.

Congestive Failure

In 1949 a report by Berger, Irwin, Rosenberg and Jackenthal described the use of a hydrogen exchange resin, Liquonex CRW, in two patients with congestive failure (19). The resin was administered for periods up to forty days. It was found that during resin administration both patients showed an excellent diuresis and mercurial diuretics were required less frequently. These findings were checked by studying the effect of discontinuing resin therapy. Following resin therapy it was found that the patients promptly began to gain weight and the frequency of mercurial injections was increased. No toxic effects were observed during resin therapy in either patient, however, the period of therapy was rather brief.

Crossfield, in 1950, treated five patients with congestive failure using both the sulfonic and carboxylic cation exchange resins (20). The resins were composed of one part calcium cycle, one part potassium cycle, and two parts hydrogen cycle. He found that none of the patients could tolerate the gastrointestinal irritation of the sulfonic resin, nor did its therapeutic effects compare well with the carboxylic resin. The carboxylic resin caused no untoward effects and in all but one case produced a significant weight loss and a lowered frequency of mercurial injections. Here again the period of administration was rather brief for full evaluation of toxic effects.

The same year, 1950, Danowski, Greenman, Mateer, and Peters conducted studies on four patients with congestive failure using an ammonium cation exchange resin, while in a similar study Kraus observed twenty two patients (21, 22). The results of both surveys were similar - all patients presented a progressive lowering of the serum carbon dioxide combining power and serum potassium levels, and all experienced a progressive weight loss. There were no clinical manifestations of uncompensated acidosis or hypokalemia in any of the patients. In view of the blood chemistry findings one would expect acidosis and hypokalemia to become manifest if treatment were continued.

Chapman and Pannill studied the effects of a combination of hydrogen and potassium cation exchangers administered to

four patients with congestive failure (23). The study was conducted over a two week period, during which daily serum sodium and potassium levels were determined. In addition, blood chloride, calcium, and carbon dioxide combining power determinations, ECG tracings, urea nitrogen determinations, and total blood base determinations were done at frequent intervals.

The serum potassium, calcium and chloride levels remained within normal limits. No appreciable change in the electrocardiographic tracings occurred, nor was there a change in the total blood base. No untoward side reactions were noted and all patients showed a progressive weight loss, up to twenty five pounds.

From this study one can conclude that the addition of the potassium form resin aided in the prevention of acidosis and prevented potassium depletion.

Martz, Kohlstaedt and Helmer studied eleven cases of congestive failure during the course of one year, 1950 (24). Their studies were rather unique in the fact that they met and apparently overcame the two most important untoward reactions seen in cases of renal impairment, acidosis and hypokalemia.

In the initial phases of their studies they found that if a hydrogen form resin was given in large enough quantities to produce a significant sodium depletion, hypokalemia resulted

within two weeks. They subsequently found that the addition of a potassium form resin would prevent the development of hypokalemia. However, it was then discovered that in some cases where there was renal impairment, the administration of this combination over a period of several weeks caused a reduction in the carbon dioxide combining power of the blood. In several cases the acidosis was severe enough to warrant the discontinuance of the resin therapy. The investigators then found that the addition of a small amount of anion exchange resin would prevent this untoward effect.

In summary of their findings, they recommended a daily sodium intake of from one and a half to three grams and a total daily dose of sixty grams of the combination of hydrogen and potassium cation exchanger and small amounts of anion exchanger. This regime produced no abnormalities in vascular electrolyte composition nor any untoward effects of any nature. One patient was carried on this regime for fifty six weeks.

Kleiber and Pickar, in 1951, evaluated the use of a combination of ammonium and potassium carboxylic resins in seven cases of congestive failure which had not responded to usual theraputic measures (25). They concluded that these patients benefited from the resin administration in the following manner: (1) Reduced mercurial diuretic requirements, (2) Decreased frequency of paracenteses, (3) Progressive weight loss, (4) More normal diet.

CIRRHOSIS OF THE LIVER

The first reported trial of cation exchange resins in the treatment of cirrhosis of the liver was conducted by Irwin, Berger, Rosenberg and Jackenthal in 1949 (19). In this study a hydrogen form carboxylic cation exchanger was used in the treatment of a fifty two year old white male with decompensated cirrhosis of the liver. It was found, after seven weeks of observation in the hospital, that the patient required mercupurin every ten days to maintain a weight level between fifty six and fifty nine kilograms.

Resin therapy was begun and after twenty two days the patient was clinically free of ascites at a weight of forty nine kilograms. However, at this time the patient was weak, anorexic and cachectic and his serum carbon dioxide combining power was 8.5 mM. per liter, serum chloride was 114 mEq. per liter and serum potassium was 2.3 mEq. per liter. The resin was discontinued and alkalizing solutions were administered intravenously. The patient did not appear critically ill but suddenly developed an aberrant ventricular rhythm and expired. The death was not explained by the investigators since it was not understood how the adicosis could have contributed to the death and the electrocardiographic tracings did not show potassium deficiency changes.

The next reported study was by Chapman and Pannill in

1950 (23). They administered a combination of the acid and potassium form carboxylic exchangers to two patients with advanced cirrhosis of the liver over a two week period. During this period of therapy the serum potassium, chloride and calcium levels remained within normal limits, there was no change in the total blood base, and the electrocardiographic tracings showed no appreciable change. Both patients showed a preogressive weight loss and displayed no untoward reactions.

This was a relatively short trial period and although it demonstrated the value of the resin in producing a weight loss, sufficient time was not allowed for the development of any untoward effects that might occur with continued therapy and maintenance.

Martz, Kohlestaedt and Helmer, in 1950, observed the effects of various types and combinations of resins in five cases of cirrhosis (24). These observations ran over a period of a year. They found that the administration of a hydrogen form resin for a period of two weeks would cause hypokalemia in most cases if the resin was given in quantities sufficient to cause a progressive weight loss. This factor was overcome by the addition of a potassium form resin. They also found that in some patients with renal insufficiency prolonged

administration of the resin combination resulted in an uncompensated acidosis. To overcome this untoward reaction, a small amount of anion exchange resin was added to the hydrogen-potassium cation exchange mixture. Using this preparation, acidosis was prevented and no untoward effects were noted. The mixture was given to one patient for a period of fifty six weeks without ill effects, but with a definite improvement in clinical condition.

Hay and Wood, during the same year, 1950, used a combination of ammonium and potassium carboxylic cation exchange resins in the treatment of three patients with cirrhosis of the liver (26). Of these three patients, one died of massive hemorrhage from esophageal varices after only four days of resin therapy. There was no response to therapy during the four days. The other two patients exhibited a marked diuresis on resin therapy. There were no untoward effects observed in either of the patients. Since the therapy was continued over a very short period of time (9 days), these observations are of no use in the evaluation of prolonged resin therapy but show that they may be of value in this condition. One of the two patients was being prepared for a spleno-renal shunt and in this capicity the drug was very useful.

NEPHROTIC SYNDROME

Experimentation with cation exchange resins has indicated that renal insufficiency is the greatest hazard in the use of these resins. However, various investigators have attempted to use various combinations of resins in cases of edema in the nephrotic syndrome. The results, as will be seen, have been encouraging in some cases.

Chapman and Pannill, in 1950, administered a combination of hydrogen and potassium carboxylic resin to two patients suffering with chronic glomerulonephritis (23). These patients were followed with daily serum sodium and potassium excretion levels. Blood chloride, calcium, carbon dioxide combining power, urea nitrogen, total base determination and electrocardiographic tracings were done at frequent intervals. Both patients showed a progressive weight loss over the two week period of therapy. There was no appreciable change in the electrocardiographic tracings or total blood base. The patients experienced no untoward effects.

This period of therapy was too short to give a good evaluation of the resin therapy. Acidosis usually develops over a period of several weeks in cases of renal insufficiency.

The same year, Hay and Wood reported on the administration of a combination of the ammonium and potassium forms of

carboxylic cation exchangers to one patient with the nephrotic stage of glomerulonephritis (26). The patient had been treated with a low sodium diet and mercurial diuretics with only limited response. The cation exchange resins were administered for a period of ten days with only a two pound weight loss. This response was very disappointing and the therapy was discontinued.

In 1951, Lippman reported on twelve patients considered to have a degenerative stage of glomerulonephritis (27). Two other patients were diabetic with Kimmelstiel-Wilson syndrome. All but two of the patients had impaired renal function according to creatinine clearance tests and of the twelve two were frankly uremic. The investigator used an ammonium carboxylic cation exchange resin. Of the fourteen patients, eleven showed an excellent diuresis and were maintained at a nearly "dry weight" for periods up to one year. Of the three who did not respond, two were unable to take the resin in adequate amounts, one of these being a frankly uremic child with nausea and vomiting. The other patient took apparently adequate doses for a sufficient period but no diuresis occurred.

The author apparently averted all untoward effects by a rather unique dosage schedule. The resin was administered in five day courses with a two day rest period between each course until a "dry weight" was approached. For maintenance,

short two to three day courses of therapy were used with every two to three pound weight gain. Lippman also found it necessary to add one gram of potassium chloride to each dose of resin if the therapy was continued for a longer period than five days. He found, however, that acidosis was generally avoided by the forty eight hour hiatus in therapy.

TOXIC EFFECTS OF ADMINISTRATION

ACIDOSIS

Since the strong basic cations, sodium and potassium, are removed from the body by the cation exchange resins, it is reasonable to fear acidosis as a complication of therapy.

Clinical studies have shown that in patients with normal renal function the acidosis is compensated by several mechanisms. It was found that there is an increase in the ratio of ammonia to urea in the urine. This ammonia serves as a substitue for sodium and potassium which normally form urinary salts with chlorides, phosphates, and sulfates. In those patients with renal insufficiency this ammonia production is deficient and the acid radicals accumulate in the body fluids (28, 29).

Hyperventilation is another process which aids the body in preventing acidosis. This process rids the body of increased amounts of carbon dioxide and thus decreases the acidity of the serum.

Most commercial preparations of the cation exchange resins contain a potassium form of the resin. This is added mainly to prevent hypokalemia, but the potassium aids somewhat in preventing acidosis.

Acidosis must be prevented, but if not prevented, detected early. With this in mind, routine urinalysis, PSP excretion,

and NPN determinations should be done on all patients prior to resin therapy. In addition, weekly serum carbon dioxide combining power determinations should be done for the first month.

If during therapy signs of apathy, weakness, anorexia, air hunger, or a fall of more than 18 volume per cent in the carbon dioxide combining power occurs, therapy should be discontinued immediately. Usually a hiatus in therapy of forty eight hours accompanied by plenty of water will clear up most cases of acidosis (27). If this does not suffice or if the patient is in a state of severe uncompensated acidosis, sodium lactate or bicarbinate may be given orally or intravenously as the case demands.

HYPOKALEMIA

Hypokalemia is another danger to be considered when cation exchange resins are used. Clinical investigations have shown that without additional potassium administration the hydrogen resin will cause hypokalemia in a period of two weeks or less (24). This condition is enhanced by the fact that the patients are usually on a low sodium diet thus decreasing the concentration of sodium in the gut and causing a relatively increased potassium concentration. Hypokalemia is rarely observed until the "dry weight" is approached but has been observed in edematous states (27).

To combat this danger, potassium form resins have been added to most commercial resin preparations (23, 24, 26, 28). The potassium form supplies enough potassium to prevent the development of hypokalemia but not a sufficient quantity to cause a hyperkalemia which is an even greater danger.

Symptoms of hypokalemia are vague and consist mainly of weakness and mental confussion (27). However, the findings of a low serum potassium level or a low voltage or absent T wave and increased QS interval on the electrocardiographic tracings give definite proof of hypokalemia (27).

The treatment of hypokalemia consists of the cautious administration of potassium chloride either orally or intravenously, whichever the case demands.

GASTROINTESTINAL DISTURBANCES

Clinical investigations have shown that epigastric distress and nausea occur more frequently with certain types of exchangers than others (28). It was found that the carboxylic resins caused less digestive disturbances than the sulfonic resins, and the ammonium and potassium forms less than the hydrogen forms. However, some patients suffer from nausea (not including those with uremia) whatever form is used.

Another gastrointestinal disturbance occasionally seen is constipation. In old and feeble patients fecal impaction

similar to that caused by a barium impaction may occur.

CALCIUM AND MAGNESIUM DEPLETION

There is little danger of calcium and magnesium depletion with the use of cation exchange resins. The reason to account for this is that the concentration of these cations in the gut is very low. Thus, since the adsorption of cations depends on concentration in addition to magnitude of charge and atomic size very little is removed from the body by the resin administration. Over a period of months or years there is a risk of demineralization because of the slow continuous drain on the mineral stores. Since the cost of supplimentary calcium and magnesium is minimal it may be advisable to give these minerals with long term cation exchange therapy (28).

SUMMARY

The use of cation exchange resins in edematous states is relatively new in the field of medicine. It was first suggested in 1946 by Dock (15). Since that time a great deal of clinical investigation has been done. From these works two major facts arise: (1) The cation exchange resins will, in most cases, deplete the body sodium and relieve edema. (2) The greatest hazard in its use is renal insufficiency.

Clinical investigations have shown that of the cation exchange resins used the carboxylic resins produced fewer gastric disturbances than the sulfonic resins. It has also been shown that none of the forms of resin, such as hydrogen potassium, or ammonium, may be given alone over a period of several weeks without untoward effects.

When the ammonium or hydrogen resins are given without the potassium form a hypokalemia will result within two weeks if given in sufficient quantities to control the edema.

If the potassium form resin is given in sufficient quantities to control the edema, hyperkalemia will result. The usual hydrogen (or ammonium)-potassium ratio is a 2:1 or 3:1 mixture.

The administration of a hydrogen (or ammonium)-potassium

cation exchange resin will secure diuresis of edema fluid or potentiate mercurial diuresis in most cases of edema due to congestive failure, cirrhosis or the nephrotic syndrome. However, acidosis will prevent the continuation of the drug in those patients with severe renal impairment unless certain precautions are taken. The acidosis results from the removal of the strongly basic ions of sodium and potassium from the body and the failure of the kidney to produce ammonia as a substitute for the lost base. The addition of the potassium form resin has helped somewhat in the prevention of acidosis but cannot prevent all cases. One proprietary cation exchanger has added a small amount of anion exchange resin and this has been reported to be very valuable in preventing acidosis(24). Another very interesting observation was made by Lippman in his study with cation exchange resins in nephrotic syndrome(27). He found that a five day course of therapy followed by a two day rest period repeated until a "dry weight" was approached prevented acidosis in most cases. These patients were then maintained with two to three day courses of therapy after a gain of from two to three pounds while not on the resin therapy.

Generally most authors claim excellent diuresis with a dosage of resin between forty and one hundred grams per day. The average dose is between forty-five and sixty grams per days in three equal doses. A dosage schedule that is too

high gives no better results in fecal sodium excretion than the optimal dose determined for each patient. A dosage that is too low results in a very much lower fecal sodium excretion than would be anticipated. Thus dosages of twenty grams or less per day are usually grossly insufficient while those above one hundred and twenty grams per day are generally highly wasteful.

The diets of the patients using cation exchange resins must be restricted in salt content, the restriction varying with the severity of the case. The greatest margin of safety and the highest sodium uptake per gram of resin is found when the patient is on a diet containing from three to six grams of salt per day.

Since the dosages of cation exchange resins are massive and they are completely insoluble, the recommended mode of ingestion is a freshly prepared liquid suspension. The preferred liquids are thick juices such as tomato juice which maintain a suspension for longer periods. The liquid should be ice cold. Children present a great problem in that no one method of preparation of the resin is accepted for a very long period of time. However, the resins may be administered in any form of vehicle, even baked in bread or pastry.

All patients must be followed closely while on resin therapy and renal function should be checked in all patients prior to therapy. During administration the patients weight should be charted carefully and frequent serum sodium, serum carbon dioxide combining power and serum chloride determinations

should be done to prevent the development of clinical acidosis. Any patient showing marked renal function impairment should be followed carefully in the hospital during resin therapy or the resin should not be used in that case.

CONCLUSIONS

1. Most cases of edema due to congestive failure, cirrhosis of the liver, or the nephrotic syndrome will respond to cation exchange resin therapy.

2. Renal insufficiency offers the greatest hazard in cation exchange resin therapy.

3. The most satisfactory form of cation exchange resin is a combination of an ammonium or hydrogen carboxylic resin with a potassium carboxylic resin in a ratio of 2:1 or 3:1.

4. Intermittent therapy and/or the addition of small amounts of anion exchange resin appears to offer the most aid in controlling acidosis in patients with renal insufficiency.

5. Renal function tests should be done on all patients prior to resin therapy.

6. Frequent serum sodium, serum carbon dioxide combining power and serum chloride levels should be done during resin therapy, especially during the first month.

7. The usual dosage of cation exchange resins is forty to one hundred grams per day in three equal doses.

8. The greatest sodium uptake per gram of resin and the greatest margin of safety is attained when the patients are restricted to a salt intake of three to six grams per day.

BIBLIOGRAPHY

1. Thompson, C.J.S., Terra Sigillata, a famous medicament of ancient times, Proc. 17th Internat. Cong. Med. 23: 433, 1914.

2. Jenny, H., Kationen and anionenumatousch an Permutit grenzflachen, Kolloidchem. Beihefts, 23:428, 1927.

3. Mattson, S., The electrokinetic and chemical behavior of aluminosilicates, Soil Sci., 25:289, 1928.

4. Wiegner, G., Some physico-chemical properties of clays. I. Base exchanger or ionic exchange, J. Soc. Chem. Ind., 50:65T, 1931.

5. Vanselow, A.P., Equilibria of the base exchange reaction of bentonites, permutites, soil colloids and zeolites, Soil Sci., 33:95, 1932.

6. Walton, H.F., Equilibria in a carbonaceous cation exchanger, J. Phys. Chem., 47:371, 1943.

7. Adams, B.A. and Holmes, E.L., Absorptive properties of synthetic resins, J. Soc. Chem. Ind., 54:1T, 1935.

8. Segal, H.L., Hodge, H., Watson, J.S. and Scott, W.J.M., A polyamine-formaldehyde resin. I. Its effect upon the pH of acidified solutions and the pH of pepsin of gastric juices in vitro. II. Its toxicity in rats: preliminary feeding tests, Gastroenterology, 4:484, 1945.

9. Martin, G.J. and Wilkinson, J., The neutralization of gastric acidity with anion exchange resins, Gastroent., 6:315, 1946.

10. Spears, M.N. and Pfeiffer, C.J., Anion exchange resin and peptic ulcer pain, Gastroent., 8:191, 1947.

11. Segal, H.L., Hodge, H., Watson, J.S. and Scott, W.J.M., III. Chronic toxicity experiments in rats, Gastroent., 8:199, 1947.

12. Fraemer, M. and Lehman, D.J., The treatment of peptic ulcer with anion exchange resins, Gastroent., 8:202, 1947.

13. Marks, J.A., An anion exchange resin for the medical management of peptic ulcer, Rev. Gastroent., 16:82, 1949.

14. Wirts, C.W. and Rehfuss, M.E., A study of the effect of an anion exchange resin on gastric and duodenal secretions and gastric emptying, J. Clin. Invest., 19:37, 1950.

15. Dock, W., Sodium depletion as a theraputic proceedure: the value of ion exchange resins in withdrawing sodium from the body, Tr. A. Am. Phys., 59:282, 1946.

16. Tompkins, E.R., Khym, J.X., and Cohn, W.E., Ion exchange as a separation method, J. Am. Chem. Soc., 69:2769, 1947.

17. Bauman, W.C. and Eichhorn, J., Fundamental properties of a synthetic cation exchange resin, J. Am. Chem. Soc., 69:2830, 1947.

18. Boyd, G.E., Schubert, J. and Adamson, A.W., The exchange absorption of ions from aqueous solutions by organic zeolites, J. A. Chem. Soc., 69:2818, 1947.

19. Irwin, L., Berger, E.Y., Rosenberg, B. and Jackenthal, R., The effect of cation exchange resins on electrolyte balance and its use in edematous states, J. Clin. Invest., 28:1403, 1949.

20. Crossfield, H.C., Cation exchange resins in the control of cardiac edema, J. Med. Soc. N.J., 47:12, 1950.

21. Danowski, T.S., Greenman, L., Mateer, F., and Peters, J.H., Ammonium cation exchange resins in cardiac edema, J. Clin. Invest., 29:807, 1950.

22. Kraus, H., The use of cation exchange resins in patients with cardiac edema, J. Clin. Invest., 29:829, 1950.

23. Chapman, D.W. and Pannill, C.H., The effect of a new cation exchange resin on edematous states, J. Lab. Clin. Med., 36:808, 1950.

24. Martz, B.L., Kohlstaedt, K.G., and Helmer, O.M., The use of ion exchange resins in the management of congestive heart failure and cirrhosis of the liver, J. Lab. Clin. Med., 36:962, 1950.

25. Kleiber, E.E. and Pickar, G., Treatment of chronic congestive cardiac failure with ion exchange resins, Ann. Int. Med., 34:407, 1951.

26. Hay, S.H. and Wood, J.E., Cation exchange resins in the treatment of congestive heart failure, Ann. Int. Med., 33:1139, 1950.

27. Lippman, R.W., Cation exchange resins in the treatment of the nephrotic syndrome, A.M.A. Arch. Int. Med., July, 1951.

28. Dock, W. and Frank, N.R., Cation exchangers: Their use and hazards as aids in managing edema, Am. Heart J., 40:638, 1950,

29. Kahn, S.S. and Emerson, K., Experiences with the use of cation exchange resins in the treatment of edema, J. Clin. Invest., 29:827, 1950.