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Cation exchange resins in the treatment of congestive heart failure

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CATION EXCHANGE RESINS IN THE TREATMENT OF CONGESTIVE HEART FAILURE

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INTRODUCTION

"Of the various disorders which afflict mankind, those of the heart and blood vessels assume first rank. In the United States these disorders represent the single greatest cause of chronic disability, and are responsible for more deaths than the next five most common causes combined. As other diseases are conquered by the progress of medical science, the proportion of persons living to the advanced ages at which cardiovascular diseases are most common continually increases. Barring the possibility of as yet unforseen discoveries leading to more effective prevention and treatment of these disorders, it can be estimated that one fourth or more of the present population of the United States will die of cardiovascular disease. Among males engaged in business and professions, the proportion will perhaps be nearer one half."

The above paragraph by Harrison and Resnik (1) serves to emphasize the importance of the treatment of diseases of the cardiovascular system in modern medicine.

The syndrome of congestive heart failure frequently occurs in many types of cardiovascular disorders during the final stages of the pathological process, and therefore, its treatment is a common problem for

both the general practitioner and the internist. The use of cation exchange resins has recently been suggested in the treatment of heart failure. Their use provides the clinician a new and potent therapeutic means of controlling body fluids and electrolytes.

It is the purpose of this paper to critically review and evaluate the use of cation exchange resins in the treatment of congestive heart failure.

DEFINITION

Ion exchange resins are insoluble, organic compounds which ionize in solution and thereby take on the functional capacity of removing one type of ion from solution in exchange for another. Anion exchangers remove negatively charged radicals. Cation exchange resins remove positively charged radicals such as sodium and potassium ions. The use of the latter in clinical medicine and particularly in congestive heart failure will be discussed.

HISTORICAL BACKGROUND

Approximately 100 years ago two English agricultural chemists, Thompson (2) and Way (3), recognized and studied extensively the principle of ion exchange as it applied to the soil. A German chemist, Gans (4),

in 1906, is credited with providing the impetus for the industrial application of the ion exchange substances. The versitility of application of the ion exchange principle was greatly increased by the discovery of the first synthetic ion exchange resins by Adams and Holmes (5) in 1934. The clinical use of anion exchange resins in the field of medicine was first suggested in 1945 by Segal and his associates (6). These resins were used for the reduction of gastric acidity in the treatment of peptic ulcer.

In 1946, Dock (7) first suggested the use of insolubie ion exchange materials for the purpose of obviating the inconvenience and monotony of a sodium-free diet in such conditions as congestive heart failure, hypertension, and cirrhosis of the liver. He reported the apparent non-toxicity of orally administered cation exchange resins in rats and dogs and demonstrated their effectiveness in increasing the fecal excretions of sodium. At that time he suggested further clinical studies on human beings with special emphasis on the effect of the resins on electrolyte metabolism.

Today, ion exchange resins have found their greatest application in the fields of analytic chemistry, industry, pharmacy, and agriculture. In medicine their usefulness is just beginning to come under

investigation, and their place will be more definitely established when improvements in synthesis result in greater specificity of performance in vivo. Significant progress toward this end continues to be made by the resin chemists, and it is likely that in the near future use of resins in investigative and therapeutic problems will greatly increase.

CATION EXCHANGE RESINS

Structure

Cation exchange resin molecules are insoluble, high molecular weight, stable, polymers arranged in a structure that resembles a crystal lattice. The cross linkages between the molecules usually consist of either methyl or phenyl groups. Each of these structural elements has the ability to bind a diffusible ion and to exchange this bound ion for one of like charge under suitable conditions of solution. In this way ions in solution with the resin may be removed from solution by exchange with ions originally held at the exchange sites. At the exchange site of each of the polymeric elements of a resin molecule is a fixed functional group of opposite charge from the exchanging ions. The functional group may be, for example, a carboxyl element with the COO- portion bearing the negative charge,

and the H+ ion the positive charge, the latter being able to exchange with any other cation to change the functional group from RCOO-.H+ to RCOO-.Na+.

Theory of Action

When a resin is placed in a solvent it tends to swell, thus facilitating the diffusion of the ions to be exchanged throughout the molecular structure of the resin. The efficiency or the exchange potential of a resin depends on how many milliequivalents of electrolyte it is able to remove from a solution and how rapidly it does this. Many factors (8) are involved in controlling this potential, and it is toward the control of these factors that the resin chemists are working in order to be able to synthesize specific resins for specific jobs. Some of these factors are (a) pore size of the molecular lattice, (b) size of the resin particles, (c) concentration of the resin in solution, (d) nature of the functional group, (e) size of cations in solution, (f) the valence and atomic weight of the cation, and (g) the pH of the solution.

The size of the pores in the cross-linked resin molecule is probably the most important single factor in the exchange potential. Since the resin acts as an electrolyte sponge, electrolytes must be able to diffuse throughout the substance of the molecule in

order to occupy all the exchange sites and saturate the molecule. Large pores permit easy diffusibility and rapid and complete saturation, whereas small pores in tightly cross-linked molecules decelerate diffusion through the body of the molecule and may limit large ions such as vitamins and other organic ions to exchange sites only on the surface of the resin.

The mesh size of resin particles is another important determinant of resin efficiency. The smaller the particle, as measured by its mesh size, the greater the exchange potential.

The higher the concentration of resin in solution the greater the exchange potential.

The exchange potential is higher if the functional group is a strong acid or a strong base than with less strongly dissociated groupings such as phenolic acid. The potential is lowest of all in the amphoteric naturally occurring resins.

Simple ions such as Na^+ and Cl^- diffuse rapidly from solution throughout the molecular matrix of a resin and saturate all exchange positions available. Larger ions such as organic acids diffuse more slowly and may be able to occupy only surface positions.

The tendency of an ion in solution to displace an ion already on the exchange position depends

on two properties, the valence and the atomic weight. Ions of higher valence tend to displace ions of lower valence. Thus, aluminum displaces calcium and calcium displaces sodium. If the valence is the same, ions of higher atomic weight tend to displace ions of lower atomic weight. Thus, potassium displaces sodium and calcium displaces magnesium. These factors are important, but it has been found that they are true only in dilute aqueous solution of a resin. At high concentrations or in nonaqueous solutions these tendencies may be reversed. This may account for the failure of animals and man to develop a negative calcium balance when fed cation exchange resins to remove sodium from the gastro-intestinal tract.

Different resins work more efficiently at different pH, this property varying with the particular resins.

Little is known about the variations in the total base concentration throughout the gut. Even less is known regarding the individual concentrations of the various cations comprising the total base. It would appear that the concentration of sodium is high enough to more than compensate for the greater affinity of the resin for potassium. Much remains to be done in order to ascertain what environmental factors within the gut

lumen are most favorable to ion exchange. The precise limits of the exchange capacity of a resin in vivo have yet to be determined. Such limits are probably determined by a variety of factors such as the amount of resin ingested, the rate of movement of resin through the gastro-intestinal tract, variations in pH throughout the course of the bowel lumen, the amount of sodium in the diet, and the rate of exchanges of sodium across the intestinal mucosa.

Types

Most of the currently produced cation exchange resins are of three main types as determined by the functional group. These types of functional groups include sulfonic acid ($SO_3^-.H^+$), carboxylic acid ($COO^-.H^+$), and phenolic acid ($O^-.H^+$). The sulfonic acid resin is a strong acid and a rapid exchanger. The carboxylic acid resin is a less strong acid and a slower exchanger. The phenolic acid resin is a weak acid and a slow exchanger.

The ion originally at the exchange site before the resin is put into solution determines the so-called "cycle" of the resin. Thus a carboxylic cation exchange resin in the hydrogen cycle will have the hydrogen ion at its exchange sites ($RCOO^-.H^+$). Some resins are now manufactured that are partially satur-

ated with potassium ions and therefore, will be designated as a carboxylic cation exchange resin in the hydrogen and potassium cycles.

There are three commercial preperations of cation exchange resins available for general use. These include Carbo-Resin (Lilly), Natrinil (National), and Resodec (Smith, Kline, and French). Carbo-Resin is a mixture of one-eighth polyamineformaldehyde anion exchange resin and seven-eighths carboxylic cation exchange resin 66 per cent in the hydrogen cycle and 34 per cent in the potassium cycle. Natrinil is a cation exchange resin of the carboxylic type, 80 per cent in the hydrogen cycle and 20 per cent in the potassium cycle. Resodec is a carboxylic cation exchanger 50 per cent in the potassium cycle and 50 per cent in the ammonium cycle.

PATHOGENESIS OF EDEMA IN CONGESTIVE HEART FAILURE

The syndrome of congestive heart failure, resulting from an initial inability of the heart to maintain an adequate blood flow to the tissues, involves a complex series of events usually occurring over a considerable period of time, the final manifestations of which include venous congestion and edema. The intermediate steps in the pathogenesis of the syndrome are

still a matter of great controversy; however, it has been generally recognized in recent years that renal factors are of the upmost significance, and play a primary role in the development of cardiac edema.

The principle abnormalities in the fluid and electrolyte pattern in congestive heart failure are (a) changes in the distribution of body fluids and (b) changes in the intracellular electrolyte compartment. The predominate abnormality in the distribution of body fluid in cardiac edema is an expansion of the volume of extracellular fluid. This expansion has usually been considered to be isotonic. Evidence for this rests upon the observation that the products of diuresis are, for the most part, water, sodium, and chloride in the same relative proportions which are found in the extracellular fluid.

Intracellular changes have also been suggested and abnormal transfers of sodium and potassium have been described in cardiac failure. Squires, Crosley, and Elkinton (9) did electrolyte studies on patients with cardiac edema and concluded that intracellular abnormalities included potassium depletion, increased osmolarity of the solutes present, and overhydration.

Before undertaking a discussion of the renal factors involved in the pathogenesis of congestive

heart failure, the normal renal mechanisms of extracellular fluid regulation should be briefly reviewed. Regulation of the volume of extracellular fluid by the kidney is controlled almost entirely by sodium reabsorption. It is generally agreed that this is a function occurring primarily in the proximal renal tubule. The capacity to transport sodium is intrinsic within the tubule cells, but the rate of transport is regulated by extrinsic factors.

The factors affecting reabsorption of sodium include (a) glomerular filtration rate and (b) hormonal secretions. In general, a decreased glomerular filtration rate causes an increase in sodium reabsorption. However, glomerular factors are considered to be insignificant in the over-all control of sodium reabsorption.

Among the hormonal factors which regulate sodium reabsorption the most important are the adrenal cortical steroids. Increased amounts of desoxycorticosterone acetate cause retention of sodium. There is also some evidence that the adrenal steroids facilitate rapid excretion of sodium when intake of that ion is high. The stimulus which controls secretion of the adrenal steroids has not been worked out. Certain investigators (10) have recently hypothesized an intracranial volume receptor or volumeter which responds to

changes in blood or interstitial fluid volume, and thus regulates secretion of the adrenal steroids and sodium reabsorption.

There are data to indicate that progesterone may also exert mild sodium retaining effects and that antidiuretic hormone, under certain conditions, inhibits sodium reabsorption.

The regulation of the electrolyte pattern and the effective osmolarity of the extracellular fluid is a function of sodium reabsorption, water reabsorption, and acid-base balance. In the final analysis, however, water reabsorption depends for the most part upon sodium reabsorption and the concentration of sodium in the extracellular fluid. Acid-base balance will be discussed only in so far as it is related to sodium reabsorption. Other electrolytes play a relatively minor role and, therefore, their contributions will not be discussed.

Water reabsorption can be divided into (a) obligatory reabsorption and (b) facultative reabsorption. The former refers to water reabsorbed in the proximal tubule and is related to the reabsorption of osmotically active solutes. The amount of water reabsorption is directly proportional to the amount of osmotically active solute reabsorbed. This osmotically

active solute consists primarily of sodium and its associated anions. Thus, sodium has an inherent priority over water in the production of edema because, if it is not absorbed from the renal tubules, the reabsorption of water is correspondingly limited.

Facultative reabsorption is a function of the distal tubule and is regulated by the antidiuretic hormone of the posterior pituitary. It has been shown by Verney (11) and O'Connor (12) that the posterior pituitary secretion of antidiuretic hormone is stimulated by changes in hydration of the cells which in turn, is controlled by the effective osmotic pressure of the extracellular fluid. It is generally recognized that the effective osmotic pressure of the extracellular fluid is usually synonymous with the concentration of sodium salts in that fluid. Therefore, water reabsorption is either directly or indirectly dependent upon sodium reabsorption.

It has been noted that under certain circumstances water is reabsorbed in excess of sodium. Thus, although for the most part the effective osmolarity of the extracellular fluid controls facultative reabsorption, it has been postulated that diminished volume may occasionally be the stimulus for water reabsorption. It has also been observed that other endocrine glands,

such as the thyroid, the anterior pituitary, and the adrenal cortex exert some influence on water reabsorption.

Acid-base balance is also involved in the regulation of the electrolyte pattern of the extracellular fluid. A carbonic acid concentration of 1.25 to 1.35 m. eq. per liter is maintained in the plasma and is regulated by respiratory mechanisms. Normally there is a stable renal bicarbonate threshold of 25 to 27 m. eq. per liter. It is well known that changes in the normal carbonic acid-bicarbonate ratio manifest changes in acid-base balance. These changes are compensated for by respiratory and renal mechanisms, thus attempting to restore the normal ratio. When the bicarbonate threshold is normal or below this level, bicarbonate is entirely reabsorbed in the proximal tubule. When the bicarbonate threshold is above the normal, the excess bicarbonate is excreted.

Moyer and Harrison (13), in discussing the pathogenesis of edema, state that in order for generalized edema of significant degree to develop, two conditions must be fulfilled: (a) The rate at which fluid enters the tissues from the blood stream must exceed the rate at which fluid leaves the tissues. (b) The fluid output of the body must be less than the fluid

intake. Briefly, these two factors can be called the tissue factors and the renal factors. The concepts involved in the former are fairly well understood but the mechanisms controlling the latter still remain obscure in certain respects.

The tissue factors determine where edema will occur, and it is possible for the tissue factors alone to lead to the development of edema in limited areas, the local increase in extracellular fluid volume being purchased at the expense of a decline in the extracellular fluid content of the remaining nonedematous parts. However, such a process can be limited only in degree, for any significant decline in extracellular fluid volume of a large portion of the body leads, through mechanisms as yet poorly understood, to retention of sodium and water by the kidney. It is evident, therefore, that the tissue and renal factors cannot be entirely separated and that the renal factor is essential in all types of generalized edema.

No extensive discussion of tissue factors will be undertaken except to briefly mention the concept of backward failure and its relation to the pathogenesis of cardiac edema. The sequence of events in backward failure as deduced from Starling's original hypothesis is essentially as follows: cardiac failure

with inadequate output, elevated venous and capillary hydrostatic pressure, transudation of fluid causing edema, decreased plasma volume, and finally retention of sodium and water by the kidney. Peters (14), without denying the importance of the renal factor in generalized edema, has recently re-emphasized the basic, well-established principles of this sequence of events and has questioned the validity of the evidence for high blood volumes in cardiac failure as hypothesized in the concept of forward failure.

In 1943 Starr and co-workers (15) and subsequently Warren and Stead (16) proposed another sequence of events to explain the edema of congestive failure. The forward theory of failure is based upon the concept of altered glomerular filtration. The sequence of forward failure is hypothesized as follows: cardiac failure with inadequate output, decreased renal blood flow and decreased glomerular filtration rate, retention of sodium and water, increased plasma volume, increased venous and capillary pressure, and transudation of fluid causing edema. Evidence for increased production of renin and vasoexcitor material (VEM) (17) and thus, further reduction of renal blood flow has also been presented. However, although altered glomerular filtration occurs quite commonly in congestive failure,

several investigators have found no correlation between the glomerular filtration rate and recompensation and decompensation. Also, in some patients in congestive failure, the filtration rate is within the normal range. This suggests that other factors which act directly upon the renal tubule may be important in congestive failure. This suggestion concurs with the concept of normal renal control of sodium reabsorption in which the glomerular filtration rate is perhaps contributory but in which altered tubular transfers are chiefly responsible.

In discussing altered tubular transfers in congestive failure the important problem is that of sodium reabsorption. In the brief review of normal renal physiology the importance of sodium and its associated anions in the regulation of volume and osmolarity of the extracellular fluid was emphasized. It was also stated that the adrenal cortical steroids were the primary stimulus for increased sodium reabsorption. In congestive failure there is much evidence for increased adrenal cortical activity. Parrish (18) has found increased adrenal corticoid excretion by bio-assay methods in the urine of patients in congestive failure. Merrill (19) has reported low sweat sodium in congestive failure patients. Thus, although the adrenal

cortical steroids are probably instrumental in the sodium retention of congestive failure, the stimulus for their action is still obscure.

Harrison and his associates (10) have postulated a volume receptor or volumeter within the cranial cavity which conditions the renal excretion of sodium. They suggest that in congestive heart failure intracranial blood volume is diminished by redistribution of blood to other parts of the body, thus stimulating the receptor. Recently Lombardo and Harrison (20) and Lombardo (21) completed experiments in which they concluded that the volume receptors postulated above are either inactive in congestive heart failure or are overshadowed by some more powerful sodium retaining mechanism.

One of the most recent theories (22) postulates that altered hepatic physiology in congestive failure may be responsible for sodium and water retention. The role of the liver is of particular significance in the inactivation of the adrenal steroid and the antidiuretic hormones. If in congestive failure the hepatic impairment were sufficient to lead to suboptimal inactivation of these hormones, increased sodium and water reabsorption would follow.

It has been pointed out that water reabsorp-

tion for the most part is dependent upon sodium reabsorption and parallels it within certain limits. Increased amounts of antidiuretic hormone have been reported in the urine of patients in congestive failure. This finding is consistent with the relation of water reabsorption to sodium reabsorption. However, the priority of sodium is not absolute. Occasionally water appears to be retained in excess of sodium. It can only be postulated under these circumstances that volume in some way also regulates water reabsorption.

In conclusion, it has been emphasized that sodium retention by the kidney is a primary factor in the pathogenesis of the edema of congestive failure, and that this sodium retention probably results from increased adrenal cortical activity. Much remains to be discovered, however, about the specific mechanisms which stimulate the hormonal control of sodium reabsorption.

RATIONALE FOR THE USE OF RESINS IN CARDIAC EDEMA

Sodium Restriction

The recognition of the importance of renal mechanisms in the fluid retention of congestive failure constitutes one of the significant advances in recent medical progress. While supportive therapy to the myo-

cardium itself will aid in elimination of excess fluid by correcting the basis for altered renal function, other measures are indicated. Physiologically, the normal kidney responds readily to changes in the composition of the body fluids, but less readily to changes in their volume. The removal of excess edema fluid must be aided by means designed to obviate this factor. It may be accomplished by deliberately disturbing the composition of the body fluids by restricting the intake of sodium. Since this substance constitutes the main factor in osmotic regulation of extracellular fluid, a reduction in its extracellular concentration, due to limited intake, will be followed by increased excretion of water as the kidney attempts to maintain normal osmotic relationships. Reduction in volume of blood and tissue fluids must follow. It should be remembered, however, that such interference with physiologic mechanisms is not without its dangers. If sodium depletion becomes excessive, the kidney will retain sodium at any cost, even to the point of cessation of adequate urine flow.

Removal of Sodium Through the Gastro-Intestinal Tract

Although the restriction of sodium intake in the form of a salt poor diet has become an accepted form of therapy in congestive heart failure, its success

is entirely dependent upon the patient's willingness to accept such a regimen. It is no easy task to prepare a varied and palatable diet which contains only 1 to 2 grams of sodium chloride. Few patients will tolerate the monotonous, tasteless low-sodium diet for more than brief intervals. Any means which would permit these patients to ingest a diet containing a reasonable amount of sodium chloride, and yet prevent the entrance of the sodium into the extracellular fluid compartment, or provide a mechanism for removal from this compartment, would be a welcome solution to this problem. The use of cation exchange resins has been suggested as a method of accomplishing this.

The studies of Visscher (23) and his associates have shown that every two hours a quantity of sodium equal to the entire quantity present in the body diffuses into and out of the gastro-intestinal tract. Cation exchangers, in equilibrium with these ions and also with ingested sodium ions, bind a certain quantity of them and thus allow their removal via the gastro-intestinal tract. The final result of this therapy, theoretically, should be the same as that of a low salt diet.

ELECTROLYTE STUDIES DURING THE USE OF RESINS

Animal Studies

Dock (7) first reported on the use of resins in animals. He found that when massive doses were given to dogs, or when resins were fed to rats as 10 per cent of the food mixture, there was no evidence of toxicity or gastro-intestinal disturbances. When resin was added to make up 10 to 25 per cent of the diet, the fecal sodium loss was greatly increased over that of the control animals. He observed that the sodium uptake in the gut was from 20 to 30 milligrams per gram of resin.

Crismon (24) measured intakes of sodium and potassium and fecal loss of these cations from 10 rats every other day for 23 days. After a 9 day control period, 10 per cent by weight of an acid treated, sulfonated polystyrene resin was added to the diet. During the control period 96 per cent of ingested sodium and 94 per cent of ingested potassium were absorbed from the gut. During high sodium intake plus resin, absorbed sodium decreased to 34 per cent while potassium absorption remained at 82 per cent. The low sodium diet containing resin was fed for an additional 10 days and the animals were killed. The mean plasma sodium level was 152 m. eq. per liter. Potassium concentrations were slightly low with a mean of 3.2 m. eq.

per liter.

In 1950 McChesney and McAuliff (25) reported on the effects of various exchange resins on the mineral metabolism of rats. All of the cationic exchange resins bound some sodium and potassium in the intestine; when fed in the hydrogen cycle they also bound some calcium, but this was not true of the resin which was fed in the ammonium cycle. About 20 to 25 per cent of the total capacity of the resin was usually utilized, with the ratio of binding of Na:K being nearly 2:1, although the dietary ratio was either 3:2 or 2:2. When a resin of the carboxylic type was fed partly in the potassium cycle, it bound sodium satisfactorily in the gut, but with less net loss of alkali to the animal than when it was fed entirely in the hydrogen cycle. At a 10 per cent dietary level the resins usually bound from 15 to 60 per cent of the sodium intake (after making due allowance for the amounts normally unabsorbed on the basal diet), and there was no outstanding difference among them beyond what could have been predicted from their rated capacities. The animals occasionally showed small negative balances of sodium, potassium and chloride on the resin regimes, particularly when their food consumption was low.

In a 3 week feeding experiment, other animals

received a diet which was very low in sodium and chloride, but adequate in potassium and calcium. In the animals receiving the resin diets some sodium and very large amounts of potassium were lost in the feces. Nevertheless, they were able to maintain positive balances of both elements. Growth was not rapid, but there was no obvious evidence of the effects of sodium depletion, nor was any revealed by analysis of serum or muscle, or autopsy. These authors reported that the resins apparently act to relieve edema almost entirely by binding exogenous sodium.

Danowski and his associates (26, 27) reported on concentration of serum constituents, stool and urinary excretion of sodium, potassium, chloride, and nitro- gen, and internal balances of sodium and potassium in dogs during periods of measured diets up to 11 days in length with and without intake of cation exchange resin ranging up to 60 grams daily. Ingestion of a hydrogen cycle resin in 14 animals increased stool losses of potassium and sodium, but not of chloride or nitrogen, to values significantly greater than in those in 23 controls. Administration of a hydrogen cycle carbox-ylic cation exchange resin to dogs, 30 to 60 grams per day for 7 to 11 days, produced a statistically signif-icant decrease in serum sodium, a rise in serum chloride

and a metabolic acidosis characterized by a fall in serum carbon dioxide content and pH. During therapy with this resin, increased amounts of sodium and of potassium were lost in stools without alteration in stool chloride or nitrogen excretion. With hydrogen resin ingestion urine volumes rose with a decrease in urinary concentrations of sodium, potassium, chloride and nitrogen; the daily output of sodium and of potassium fell simultaneously with the increased losses in stools. Hydrogen cycle resin administration lowered the total amount of sodium in the extracellular compartment without producing any statistically detectable change in the external balances of this cation. Negative external and cell balances of potassium increased significantly during hydrogen resin therapy. These were related in part to the particular affinity of the resin for potassium and in part to a less than completely compensatory decrease in the urinary excretion of this element.

Ch'en and Freeman (28), after studies of the removal of sodium, potassium, and calcium from the alimentary canal of rats by hydrogen cycle resins, concluded that these ions can be removed from the animal body in significant amounts by the ingestion of cation exchange resins. The relative affinity of the resin

for different cations and the cation content of the diet both influenced the extent to which various cations were removed from the body by the resin. The in vitro and in vivo uptake of sodium by hydrogen cycle resins was suppressed by calcium and potassium ions. A high calcium content in the diet markedly interfered with the uptake of potassium and sodium by the resin. These authors reported that their experiments indicate that it may be possible to selectively remove cations from the body by proper control of the cation content of the diet and the form and amount of ingested resin.

In 1952 McChesney (29) reported on the studies of sulfonic and carboxylic types of resins in rats. Evidence indicated that both resins removed sodium, potassium, calcium, and magnesium from the food, but no amino acids, thiamine, or riboflavin. The fecal iron output of the resin-treated animals was slightly greater than that of the controls but was insignificant in terms of m. eq. per gram of resin. Evidence based on the changes in acid-base balance resulting from feeding various proportions of the sulfonic resin in the sodium or potassium cycle indicated that its total uptake of fixed base was 2.4 m. eq. per gram. It was suggested that for both resins the total uptake is the resultant of an equilibrium established by the competition of all ions, in-

cluding those released from the resin in the exchange. The ratio of sodium to potassium uptake of the resins always exceeded the dietary ratio of these elements. These authors stated that this does not support the idea that the exchange reaction is limited to the upper portion of the small intestine.

Heming and Flanagan (30) reported experiments in dogs which demonstrated that a polycarboxylic cation exchange resin did not bind any significant amount of sodium in the stomach nor in the first 3 feet of the intestine. In fact, cations (potassium) bound to the resin when ingested were released by the acid in the stomach and not recombined in the intestine. These authors stated that this would indicate that the sodium which the carboxylic type resin carried out in the stool was removed from intestinal secretions rather than from dietary sources.

Electrolyte changes resulting from the use of exchange resins in laboratory animals may be summarized as follows: (a) Fecal excretion of sodium, potassium, calcium, and magnesium were definitely increased during resin administration, although one investigator reported that this was not true of calcium when the ammonium-cycle resin was used. (b) There was no evidence that nitrogen, chloride, amino acids, ribo-

flavin, thiamine or iron were removed by resin administration. (c) Some investigators reported that acidosis, as evidenced by a decreased carbon dioxide content and decreased pH, resulted from use of resins. (d) Some investigators reported increased serum sodium levels and others reported decreased levels as a result of resin administration. (e) Increased serum chloride levels and decreased serum potassium levels were found. (f) In several studies small negative balances of sodium and potassium were reported. (g) There was some disagreement as to whether exogenous or dietary sodium alone is removed by the resins or whether the sodium of intestinal secretions is also removed.

Clinical Studies

Irwin, Berger, Rosenberg, and Jackenthal (31) in 1949, using an ammonium-saturated sulfonic resin, demonstrated by balance studies its effect on serum, fecal and urine electrolytes in both normal human controls and in subjects with edema resulting from congestive heart failure and cirrhosis of the liver. It was observed that sodium was retained effectively in the gastro-intestinal tract and excreted in the stool. Potassium was removed by the resin in amounts sufficient to cause significant lowering of the serum potassium and clinical hypokalemia. Loss of calcium was not found

to be great, but was considered to be a potential hazard, as was the possibility of clinical acidosis from loss of base, despite increased renal excretion of ammonia.

In the same year Cobbey, Williams, MacRae, and Towery (32) reported on cation exchange resins given to normal subjects and patients with edema. Investigations were made for changes in the balance of water, sodium, potassium, calcium, and magnesium. The use of resins markedly increased the excretion in the stools, of sodium, potassium, calcium, and magnesium. There was a tendency for a decrease in excretion of these elements in the urine. The increased excretion in the stools was not associated with a proportionate decrease in the urine. Resins promoted a marked increase in ammonia and titratable acidity in the urine.

The following year Currens, Counihan, and Rourke (33) did balance studies on 2 patients receiving exchange resins. Significant increases of serum chloride and decreases of serum carbon dioxide were observed. Serum potassium decreased slightly. Serum sodium and calcium were not appreciably altered. The striking observations from the balance studies were the loss of potassium and retention of chloride. One patient was observed to be in positive sodium balance and the other

patient observed to be in negative sodium balance during the administration of resin. A negative calcium balance was observed in 1 patient.

Danowski and his associates (26) did 10 complete balance studies including control periods with ordinary, moderately increased, and markedly restricted intakes of sodium in 4 human subjects during 87 days. It was observed that carboxylic exchange resins increase stool excretion of ingested sodium and potassium, remove sodium and potassium from gastro-intestinal secretions, and induce prompt diuresis of edema when used in conjunction with low sodium regimen. Diuresis was attributable to marked restriction of sodium intake, gastro-intestinal loss of extracellular sodium, and acidifying effects associated with the administration of the hydrogen cycle resin. Losses of potassium in stools increased significantly during resin therapy. This was frequently associated with losses of total body potassium and slight decreases in serum potassium concentrations.

In 1950, Kahn and Emerson (34) tested a carboxyl and a sulfonate exchanger for their ability to remove sodium and water in man. The resins were administered orally in doses of 20 to 100 grams daily. In 5 patients receiving diets containing less than 1 gram

of sodium, approximately 0.3 m. eq. of sodium and 1.5 m. eq. of potassium were removed in the stool per gram of resin administered. The increase in total fecal calcium excretion varied from 0 to 3 m. eq. per day during resin administration. By mixing equal parts of a carboxyl resin saturated with potassium and one saturated with ammonia it was found possible to prevent excessive deprivation of potassium without, at the same time, interfering with the removal of sodium. Urinary ammonia excretion was measured in 3 patients before, during and after resin therapy. In 2 of these in whom renal function was normal, a marked increase in urinary ammonia occurred during resin administration. Urinary ammonia failed to rise in the third patient, in whom there was severe renal damage, and subclinical acidosis developed.

Chapman and Pannill (35) studied the effects of oral administration of cation exchangers (carboxylic acid resins partially in the potassium cycle) on electrolyte balance in 10 subjects who were fed a constant diet of 6 grams of salt. Serum potassium, calcium and chloride levels tended to remain within normal limits. In some there was a reduction in serum sodium levels. Urinary sodium excretion was greatly decreased while urinary potassium excretion was increased. No appre-

ciable change in EKG tracings occurred, nor was there a change in total blood base. By the addition of the potassium resin the hazard of potassium depletion was apparently eliminated. No acidosis was encountered.

Hay and Wood (36) reported on 10 patients studied from 3 to 180 days and concluded that the administration of ammonium cation resin reduces both sodium and potassium excretions in urine, that hypokalemia following ammonium cation resin therapy does not occur with the ammonium-potassium cation resin, that resultant ammonium chloride absorption following administration of these resins interferes with base absorption and leads to a mild to moderate acidosis, and that effective plasma chloride levels are maintained.

McChesney (37) reported on the effects of mixed exchange resins on anion and cation metabolism. He stated that the most striking effect observed is on phosphate metabolism. The cation exchanger increased phosphate absorption while the anion exchanger decreased it. Chloride metabolism was only slightly altered by the basic resins and in some cases, the effect may be attributable to an abnormal retention of water in the intestine.

Voyles and Orgain (38) studied the effects

of long-term continuous therapy with a cation exchange resin in a selective group of patients suffering from severe, long standing congestive heart failure who had responded poorly to conventional measures of therapy. Extremely low 24 hour urine sodium excretion levels were noted. Serious serum electrolyte disturbances were not encountered during the administration of resin in its ammonium-potassium cycle.

In 1952 Elkinton, Squires, and Klingensmith (39) studied electrolyte exchanges in 4 patients with edema due to congestive heart failure during the administration of cation exchange resin. They concluded that (a) the fecal excretion of sodium and potassium was increased, (b) the pure ammonium resin removed more sodium than the ammonium plus potassium resin, (c) in most periods, the excess of sodium over chloride in the stools was more than equaled by the excess of chloride over sodium in the urine, (d) except in 1 patient with an irrigated colostomy, the fecal excretion of sodium did not greatly exceed the dietary intake of the ion.

Bonner (40) in electrolyte balance studies in normal persons receiving cation exchange resins concluded that on a sufficiently low sodium intake a negative sodium balance may be obtained by marked increase

of fecal sodium loss. Potassium loss was prevented by potassium supplements.

The clinical effects of cation exchange resins upon electrolyte balance both in normal subjects and in patients in congestive failure may be summarized as follows: (a) Investigators agreed that there is an increase of sodium, potassium, calcium, and magnesium excretion in the stool. (b) They also agreed that there is a decreased urinary excretion of the above named cations along with an increase in the ammonia and titratable acidity of the urine, the latter substances suggesting an acidotic tendency. (c) Several early investigators reported hypokalemia but agreed that use of a resin partially in the potassium cycle, for the most part, eliminated this condition. (d) Most investigators reported no important changes in the serum calcium. (e) There was general disagreement concerning the effect of resins upon the serum sodium, but the values reported were usually normal or slightly decreased. (f) There was also disagreement concerning the effect of resins on the serum chloride, but most investigators reported normal to slightly increased values. (g) One investigator reported that the cation resins caused increased phosphorous absorption.

COMPLICATIONS OF RESIN THERAPY

Acidosis

Metabolic acidosis is generally recognized as a frequent though not serious complication of resin therapy. During administration of the cation resins only basic substances are removed from the body fluid, and large amounts of ionic hydrogen and ammonium are retained. These ions combine with chloride ions resulting in an acidosis similar to that produced by the ingestion of large amounts of ammonium chloride.

The renal, respiratory, and endocrine status of the patient will influence the degree of acidosis and the metabolic reactions which occur. These processes may be reflected in changes in the serum electrolyte levels. Patients ingesting the resin may have a decrease in the carbon dioxide combining power, an increase in the chloride, and an elevation of the urea nitrogen of the blood. If renal function is adequate, increased urinary ammonia and titratable acid production, and chloride excretion will compensate for the acidosis. However, if renal function is impaired and acid and ammonia production and chloride excretion are reduced, severe acidosis may develop.

Klingensmith and Elkinton (41) reported that in their group of patients treated with resin therapy

only one chloride value was above 110 m. eq. per liter and one carbon dioxide value below 15 m. eq. per liter. Acidosis in terms of these measurements was not a serious or frequent complication. In none of this group was there any clinical evidence of acidosis.

Aaron and Weston (42) stated that in their series of cases all patients demonstrated a mild acidosis, but with continued use of the resin this generally was compensated. They observed that when the serum carbon dioxide is above 20 m. eq. per liter (44 volume per cent), resin therapy need not be discontinued. However, persistent nausea or vomiting, or severe acidosis with the carbon dioxide below 20 m. eq. per liter, is an absolute contraindication to the continued use of the resin. They reported that by including some resin in the potassium cycle, as in Carbo-Resin, additional cation is furnished which may help prevent acidosis.

Wood, Ferguson, and Lowrance (43, 44) studied acidosis in 23 patients. Of these patients 15 had a carbon dioxide combining power below 20 m. eq. per liter, the lowest being 11 m. eq. per liter. On a number of occasions they noted that the plasma bicarbonate fell slightly to moderately, but returned to more normal levels with a continuation of therapy. In no instance

did the acidosis appear to be a clinical hazard where renal function was adequate, and its value in the potentiation of mercurial diuresis was helpful. The potassium form of the resin mixed with the ammonium form in proper proportion offset to an appreciable extent the loss of fixed base and partially prevented acidosis.

Callahan, Frank, Kraus, and Ellis (45) stated that in their experience compensated acidosis occurred not uncommonly with all cation exchangers, but was partially reduced by the inclusion of potassium in the exchange position. They warned that unrelated renal impairment, with reduced capacity for ammonium production, seriously predisposes to uncompensated acidosis.

Feinberg and Rosenberg (46) reported that 4 of their patients showed no significant changes in the carbon dioxide combining power attributable to resin therapy. Compensated acidosis developed in 2 patients. The other patient developed a clinical picture of apathy, weakness, stupor, and anorexia with a fall in carbon dioxide to 11 m. eq. per liter which was probably a severe uncompensated acidosis. They stated that this patient had some impairment of kidney function and that resin dosage may have been excessive.

Thus, although metabolic acidosis occurs frequently during resin administration, it is usually not

severe and serves to potentiate the diuretic action of mercurials. Resins which are partially in the potassium cycle help to prevent this complication. Impaired renal function of long standing congestive failure or unrelated impaired renal function prevents compensation and seriously predisposes to severe acidosis.

Potassium Depletion

Hypokalemia in patients on resin therapy originally presented an important complication but through the incorporation of a potassium salt in the resin itself, this problem, for the most part, has been eliminated. It is well known that normally the resin uptake of potassium exceeds that of sodium. Thus, with the use of resins in the hydrogen or ammonium cycle, potassium depletion becomes a distinct danger. However, with resins partially in the potassium cycle enough of this ion is supplied to prevent hypokalemia.

Hypokalemia during resin therapy may be manifested by digitalis toxicity. Several investigators have commented on the relationship of potassium to cardiac irritability and its possible antagonistic effect to ventricular irritability produced by digitalis. Toxic amounts of digitalis usually displace potassium from cardiac muscle under experimental conditions; this displaced potassium may be replaced by

raising the serum potassium level.

Klingensmith and Elkinton (41) stated that hypo- or hyperkalemia were not frequent complications of resin therapy in their group of patients, and insofar as the serum level reflects the cellular stores of the ion, deficit or excess of total body potassium did not occur to a serious extent. There were no clinical signs of changes in potassium concentration.

Aaron and Weston (42) stated that because the cation exchange resin in the hydrogen cycle also removes potassium from the gastro-intestinal tract, a mixture containing resin in the potassium cycle was given to prevent potassium depletion. As additional prophylaxis against negative potassium balance, all their patients were instructed to drink at least two glasses of orange juice daily, which supplied about 20 m. eq. of potassium. None showed evidence of potassium depletion. They further stated that resin therapy should be discontinued in the presence of vomiting or severe diarrhea, conditions which may produce considerable losses of potassium. When chemical data are unavailable, electrocardiographic evidence of hypopotassemia or increased sensitivity to digitalis may be used as an index of negative potassium balance. In their study, neither was encountered.

Dock and Frank (47) stated that the potassium exchanger offers special advantages, since its use provides a base capable of preventing acidosis as well as potassium depletion. The sodium uptake per gram may be somewhat less than that with ammonium or hydrogen exchanger, and some risk of hyperpotassemia must be anticipated. However, with good renal function the danger is not great.

Wood, Ferguson, and Lowrance (43, 44) reported that depletion of potassium was not a troublesome feature with the use of the ammonium-potassium form of the resin. The lowest serum potassium level noted fell within the range of normal, namely, 3.2 m. eq. per liter. They further stated that normal serum potassium levels are not proof against potassium depletion, but continued positive urinary potassium excretion offers added evidence that adequate potassium was available to the patient. Clinical evidence of hypokalemia was suggested in only 2 of their patients, in whom digitalis toxicity, unexplained by edema loss alone, developed.

Feinberg and Rosenberg (46) stated that despite the fact that the resin they used contained 20 m. eq. of potassium per 15 grams of resin, there was a moderate fall in serum potassium at some time during

the course of therapy in 4 patients. Only in one case, however, was this of clinical significance. Hypokalemia in this patient was associated with evidences of digitalis toxicity.

Emerson, Kahn, Vester and Nelson (48) stated that since most resins remove more potassium than sodium, at least 1.3 m. eq. of potassium must be supplied per gram of resin administered.

Thus, from these reports it can be concluded that use of a potassium-cycle resin, for the most part, prevents the complication of potassium depletion.

Sodium Depletion

As a result of a low sodium diet and removal of sodium through the gastro-intestinal tract, one of the possible complications of prolonged resin administration is sodium depletion and the low salt syndrome. Although the occurrence of this syndrome is infrequent, the physician must be alert to its recognition and possible dangers. Patients with this syndrome may complain of weakness, myalgia, nausea, and vomiting. They may also have oliguria. These symptoms, of varying severity, may or may not be associated with depression of the serum levels of sodium, potassium, or chloride or elevation of the blood urea. These patients usually respond immediately to hypertonic salt solutions.

Hay and Wood (36) found that serum sodium levels tended to decline with resin therapy, but reported that in their experience no serious sodium depletion was produced.

Klingensmith and Elkinton (41) stated that in their patients the mean serum sodium level was higher, not lower, than before therapy and only 4 values were 130 m. eq. per liter or below. They concluded that the small proportion of determinations in this range, the virtual absence of severe azotemia, and the failure to observe clinical signs and symptoms of peripheral vascular collapse were strong evidence that sodium depletion was not a serious complication in their series of patients.

Aaron and Weston (42) reported that although sodium depletion is another potential hazard of sodium-removing resin therapy, in 8 of 10 patients the serum sodium concentration did not significantly change. However, after 1 month of resin therapy, 1 patient was hospitalized with symptomatic hyponatremia. The resin probably contributed to this episode, but she previously and subsequently showed hyponatremia with mercurial injections and salt restriction without resin therapy. They further stated that the usual clinical signs of the low salt syndrome are not specific and that it is

dangerous to omit serum electrolyte determinations in patients receiving resin therapy.

Wood, Ferguson, and Lowrance (43, 44) reported that the low salt syndrome occurred twice in their studies. In 1 patient, during resin therapy, the serum sodium was 139 m. eq. per liter, with a low plasma chloride of 86 m. eq. and a serum potassium of 3.6 m. eq. per liter. The blood urea rose, and the patient appeared to be quite sick but responded to hypertonic salt intravenously and potassium chloride by mouth with subsequent diuresis, restoration of normal blood urea levels, and return of appetite. It was their impression from this and other experiences that it is inadvisable to administer the cation resin to patients who are not eating well and to patients with renal insufficiency.

Feinberg and Rosenberg (46) in their treatment of congestive heart failure with exchange resins reported that 1 patient developed a low serum sodium while on resin therapy. Extremely hot weather appeared to play a role in the development of this episode of salt depletion.

Thus, sodium depletion is an infrequent but dangerous hazard of prolonged resin therapy and its possibility must always be kept in mind.

Calcium Depletion

Calcium depletion during resin administration is not a significant complication unless therapy is continued for prolonged periods of time. Although in vitro all resins have a greater affinity for calcium than for potassium, the monovalent ions are present in the intestinal tract in greater quantity than the divalent ones. Therefore, the quantity of calcium removed through the gastro-intestinal tract is probably minimal. However, over long periods there is the possibility of slow depletion of the body stores of this element.

Several investigators (36, 41, 46, 47, 49) reported that calcium depletion either was not encountered, or occurred only after prolonged resin administration (months or years). Some workers suggested that since supplementing the dietary intake with calcium is so simple and inexpensive, it should be regularly instituted when therapy is continued for more than a few weeks.

Thus, when resin therapy is continued for long periods, calcium depletion is a distinct possibility, and in such cases calcium supplements should probably be added to the diet.

Depletion of Other Substances

No important deficiencies of magnesium, iron, vitamins, or amino acids have been reported during the administration of resins in clinical therapy (41, 46, 47, 48, 49). However, experimental studies on deficiencies in both animals and man are almost entirely lacking.

Urinary Casts

The presence of urinary casts has been reported in patients on resin therapy. Apparently the casts are associated with the acidosis and acid urine that usually result from resin administration. No serious complications have resulted.

Friedman and associates (50), who did considerable work on this subject, reported that all patients, normal human beings, and experimental animals when fed sufficient amounts of the ammonium exchange resin showed numerous granular urinary casts. The number of casts varied directly with the aciduria which the resin produced. The average therapeutic dose of the resin resulted in a urinary pH of 5.5 to 6, and the number of casts produced was 10 to 30 per low power field. Discontinuing use of the resin resulted in the disappearance of these casts within a day or two. They stated that in no instance did any demonstrable deleterious

effect develop from the presence of these casts.

Thus, urinary casts appear only as an incidental finding during the use of exchange resins.

Impalatability

One of the practical problems that has arisen in resin therapy is the impalatability of the resin preparations. Many patients dislike the resins because of their taste, bulkiness, and insolubility. However, if the resins are ingested correctly, most patients, realizing the clinical benefits, are willing to overlook this minor inconvenience.

Voyles and Orgain (38, 51) reported that although some of their patients objected to the taste of the resin in earlier forms, more recent preparations have proved more palatable. In general, patients sick enough to need this form of therapy did not object seriously to the taste or bulkiness of the preparation. They suggested that the powdered resin may be mixed with cold fruit juice, water or milk, or with a solid food such as cereal or mashed potatoes.

Hay and Wood (36) stated that one of the practical problems that has arisen concerning the use of resins is their impalatability and that this can be circumvented by mixing with certain foods or by suspension in relatively heavy liquids such as tomato juice.

Friedman (49) reported that the taste, consistency, and the bulk of the various exchangers have made them difficult for some patients to ingest.

Conn and Kissane (52) reporting on the treatment of 30 patients with exchange resins stated that many patients at first complained of difficulty in swallowing the powder, but this obstacle was not insurmountable as they soon learned to suspend the powder in a small amount of liquid and drink it quickly. They stated that after their patients experimented with different liquids, the consensus was that grape juice was the best vehicle for disguising the taste and texture of the resin.

Wood, Ferguson, and Lowrance (43, 44) stated that the taste of the ammonium-potassium cation resin Resodec, though not pleasant, is certainly not prohibitive. They observed that although a few patients objected strenuously to the taste, they did not find this to be a serious handicap, and those sick enough to require the resin generally overlooked this relatively minor inconvenience.

Feinberg and Rosenberg (46) stated that most of the patients complained of the gritty taste of the powders but were more than willing to continue the medication when the clinical benefits following its use

became apparent.

In summary, impalatability of resins is a practical complication of resin administration. It is hoped that in the near future manufacturers will eliminate this problem by making available more palatable products.

Gastro-intestinal Disturbances

There are many reports in the literature about the gastro-intestinal disturbances encountered during the ingestion of cation exchange resins. Constipation is one of the most common complaints and is usually easily controlled. Fecal impaction has occurred only occasionally. Abdominal cramps and diarrhea have been noted by some investigators. Anorexia, nausea, and vomiting occur not uncommonly. It is generally agreed that these disturbances are occasionally severe enough so that therapy must be discontinued in some patients.

Voyles and Orgain (38, 51) reported that most of their patients required mild laxatives to overcome the tendency toward constipation caused by the bulk and consistency of the resin in the lower bowel. Fecal impaction was not encountered and gastro-intestinal irritation was not a serious problem with the ammonium-potassium form of the resin.

Hay and Wood (36) stated that one of the practical problems that has arisen concerning the use of resins is their tendency to produce gritty, constipating stools.

Callahan, Frank, Kraus, and Ellis (45) reported that gastro-intestinal complaints have been a major limiting factor in the use of cation exchange resins. Not uncommonly they were severe enough to terminate therapy. The carboxylic resin used in their study showed a high incidence of such toxicity, requiring cessation of therapy in 7 of the patients. Gastro-intestinal symptoms were somewhat less common in the group treated with the sulfonic resin.

Friedman (49) reported that the sulfonic resin in powder form has a constipating action. He further stated that carboxylic resins, both hydrogen and ammonium forms, because of their consistency and greater bulk, are even more constipating and produce a putty-like stool. One of his patients while taking a hydrogen carboxylic resin had a fecal impaction.

Klingensmith and Elkinton (41) reporting on the clinical complications in 34 patients stated that gastro-intestinal intolerance was the principal type of complication. Increase in the size and firmness of the stool was noted by almost all their patients. Con-

stipation causing a complaint on the part of the patient was observed in 7 patients and was of sufficient severity in 1 of these to require temporary discontinuation of the therapy. Abdominal cramps with or without diarrhea were noted in 6 patients and were sufficiently severe to necessitate discontinuation of therapy permanently in 2, and temporarily in 3 patients. Anorexia and nausea without vomiting were observed in 9 patients and in 2 of these were sufficiently severe to stop the therapy. Treatment was discontinued in patients who vomited the resin when it was initially administered. Thus, of the total group of 34 patients, 20 displayed one or more undesirable effects of resin therapy. Such therapy was interfered with in 11, and permanently discontinued in 5 patients.

Aaron and Weston (42) reported that not every patient can tolerate resins well, and some gastro-intestinal symptoms, such as anorexia, nausea, constipation, and occasionally diarrhea, generally develop. He stated that the severer signs of gastro-intestinal irritation can often be avoided either by starting with small amounts and gradually increasing the dosage or by intermittent administration. Constipation was the most frequent and annoying symptom and was controlled by occasional enemas, administration of methylcellulose

or other mild laxatives, and increased fluid intake.

Wood, Ferguson, and Lowrance (43, 44) reported that with the ammonium-potassium form of the cation resin (Resodec) relatively little gastro-intestinal irritation occurred. In 2 of their 35 patients some nausea and vomiting followed the ingestion of the resin. Rectal irritation with a slight burning sensation of the rectum was a common complaint, but this was minor in all instances. They did not encounter fecal impaction in the moderate dosage recommended. Diarrhea occasionally set in but disappeared with curtailed dosage. It was their impression that unfavorable gastro-intestinal effects previously reported may have been due to larger dosage.

Feinberg and Rosenberg (46) stated that the resin was administered to 1 patient who had to discontinue the medication after a few days because of much nausea and vomiting. Except for this case and a transient episode of nausea and vomiting in one other case there were no complaints of nausea, although some of their patients took resin for almost a year.

Thus, gastro-intestinal disturbances during resin administration are fairly common and require discontinuance of therapy in some patients. However, more recent reports of decreasing gastro-intestinal diffi-

culties with the newer preparations and with a moderate dosage are very encouraging.

USE OF RESINS IN CONGESTIVE HEART FAILURE

Review of the Literature

Irwin, Berger, Rosenberg, and Jackenthal (31) first reported experiments with cation exchange resins on patients in congestive heart failure. They concluded that the principal of the use of cation exchange substance was sound in that dietary sodium was retained in the gastro-intestinal tract and excreted in the stool. In their series of cases they reported a diuresis of existing depots of fluid which did not reaccumulate while the resin was being administered.

Since the first use of resins in congestive failure, numerous other investigators (32, 33, 34, 43, 48, 49, 55, 56, 57) reported that a majority of patients able to take the resin responded by diuresis, weight loss, and clinical improvement in the other signs and symptoms of cardiac failure. They also observed that the edema did not reaccumulate and the other symptoms did not recur as long as the resins were administered.

Several workers (38, 41, 42, 45, 46, 51, 52, 53) observed that in addition to controlling the symptoms of congestive failure the use of resins also lower-

ed the requirement of mercurial injections necessary to keep patients symptom-free. They reported that in some patients the necessity for these injections was entirely eliminated.

Certain other observers (35, 41, 45, 52, 53) reported that in many patients the use of resins made possible liberalized sodium intake without causing increased signs and symptoms of cardiac failure.

Elkinton, Squires, and Klingensmith (39) and others (36, 44, 54, 58) reported that the resin may also be a useful adjunct in the treatment of refractory cases of congestive failure by potentiating or initiating the action of mercurial diuretics on the renal tubules. The mechanism and conditions for such potentiation are at present unknown.

Voyles and Orgain (38, 51) and a number of other investigators (41, 46, 49, 52, 53) reported that certain patients responded very well to prolonged, continuous resin therapy (6 months or longer) remaining nonedematous and symptom-free during those periods.

In an analysis of 22 different series of patients reported by investigators whose results are reviewed in this section, it was found that a total of 269 patients in congestive failure were treated with cation exchange resins over a long enough period to

evaluate their effectiveness. Of the total number of patients treated, approximately 87 per cent showed clinical improvement. Approximately 10 per cent of all patients who started resin therapy could not continue because of the impalatability of the resin or because of the gastro-intestinal disturbances resulting from resin administration. Thus, from a review of the literature, the results of resin therapy in congestive heart failure, for the most part, have been beneficial.

Dosage and Methods of Administration

The dosage and methods of administration of cation exchange resins have been fairly well established. It must be remembered, however, that the dosage of resin and the diet to be recommended during its administration depends somewhat on the degree and duration of the edema and the patient's initial reaction to resin therapy. The resin appears to work at full capacity in the normal person who does not have edema. In the patient with congestive heart failure, however, the amount of sodium bound by the resin appears to be somewhat lower, the reason for this remaining obscure at the present.

The dosage of resin is usually 15 grams in fruit juice after each meal, making a total of 45 grams daily. An additional 15 grams daily appears to offer

little if any advantage. Only an occasional patient will profit by a larger dosage of cation resin, and more than a total of 60 grams daily is probably unnecessary. Since the capacity of cation resin is limited in this dosage to the fixation of 50 to 100 m. eq. (1,150 to 2,300 milligrams) of sodium daily, the patient should be on a moderately low sodium diet of 1,000 to 1,200 milligrams of sodium daily. A cation resin must not be expected to fix the large amounts of salt in a regular unrestricted diet. However, the difficulty in preparation of a 500 milligram sodium diet as compared to a 800 to 1,600 milligram sodium diet is such that there is a very real advantage in the use of resin. A few instances of severe congestive heart failure may require still further dietary restriction to 500 milligrams of dietary sodium daily (1.25 grams of salt) keeping the resin dosage at 15 grams of resin 3 or 4 times daily. For certain other patients who have been dependent on regular injections of mercury prior to the use of resin, it has been found that, once they can be brought out of the edematous state, it may be possible to maintain them edema-free on a slightly smaller dose of resin, namely, 15 grams twice daily.

Wood, Ferguson, and Lowrance (43, 44) stated that a bedtime dose of 15 grams of resin has not proved

salutary in their experience. When larger dosage is required, it should be given after the regular meals rather than at bedtime. They also state that after various trials, it appears wiser to administer the cation resin intermittently, 4 days on and 3 days off. It has been noted that restriction of sodium absorption continues 1 to 5 days after the resin dosage has been discontinued, the lag averaging about 3 days. Many patients appreciate the 3 days without resin and appear to get along somewhat better on this schedule.

The taste of the resin is not pleasant, and it is best to take it in fruit juice, preferably one-half glass of grapefruit juice, stirred or shaken well and swallowed immediately. Most investigators report that although a few patients object strenuously to the taste, they have not found this to be a serious handicap, and those sick enough to require the resin generally overlook this relatively minor inconvenience.

In summary, it can be stated that cation exchange resins have been used by many investigators in the treatment of congestive heart failure and that for the most part, this form of treatment has been beneficial. Numerous reports have been presented indicating that a large percentage of patients treated with resins showed clinical improvement. A certain number

of patients were unable to tolerate therapy because of impalatability and gastro-intestinal disturbances. The beneficial results of resin therapy in congestive failure and the dosage and methods of administration may be summarized as follows: (a) Edema and other symptoms of failure were eliminated or diminished and recurrence of symptoms and reaccumulation of edema were prevented. (b) A marked reduction of mercurial injections was possible. (c) Only moderate, rather than marked, salt restriction was required. (d) In patients who had become refractory to the usual methods of treatment (sodium restriction and mercurial diuretics) potentiation or initiation of the action of mercurial diuretics on the kidneys by the resins was noted. (e) In some patients the prolonged, continuous use of resins was successful. (f) The best tolerated and most effective dosage of resin was found to be 15 grams after each meal mixed with fruit juice. (g) An intermittent schedule of administration consisting of 4 days on the resin and 3 days off was found to be most satisfactory.

CONTRAINDICATIONS OF RESIN THERAPY

From the previous discussion of the complications of resin therapy it is not difficult to hypothesize the possible contraindications of resin adminis-

tration. Resins are definitely contraindicated in the following circumstances: (a) patients with renal insufficiency of an appreciable degree, (b) patients who are not eating well, and (c) patients exhibiting signs of the low salt syndrome.

Patients with more than a mild degree of renal insufficiency are usually poor candidates for resin therapy because of the danger of uncompensated acidosis. This may result from failure of the kidneys to maintain acid-base equilibrium by the formation of ammonia. Generally speaking, nitrogen retention in the blood should be considered a contraindication to the use of resins. If there is any doubt about kidney function further laboratory studies are indicated.

Patients not eating well should be given resin with caution, and it should be stopped immediately if for any reason the patient stops eating. Under these circumstances, resin binds circulating cations entering the bowel from the extracellular fluid, leading to serious disturbances in electrolyte balance.

Resins are contraindicated in any patient who exhibits signs and symptoms of the low salt syndrome, and if they are being administered at the time the syndrome manifests itself, they should be discontinued at once. The patient must be watched even more closely

during extremely hot weather when excessive loss of sodium through sweating makes hyponatremia a distinct risk. Failure of mercurial diuresis during the course of resin administration may be indicative of the low salt syndrome.

INDICATIONS FOR RESIN THERAPY

Indications for the use of cation exchange resin therapy are limited to those conditions in which sodium would ordinarily be restricted in the patient's diet. However, to be more specific, there are certain types of patients in congestive failure who respond to resins more readily than others. These specific indications are listed as follows: (a) Patients with long standing congestive failure who have become refractory to the conventional methods of therapy. (b) Patients unable to adhere to diets rigidly restricted in sodium or unable to reach a suitable level of sodium restriction. (c) Patients in whom mercurial diuretics have not been effective in promoting diuresis.

Severe heart failure which has been managed with difficulty by conventional measures may be greatly improved by the additional use of exchange resin therapy. It should be emphasized that in these cases resin is an adjunct to conventional measures, and not a re-

placement, although by its use the need for mercurial diuretics may be diminished or eliminated and less rigid dietary sodium restriction may be required.

There are occasional patients who, despite the knowledge of serious consequences, are not able or willing to adhere to diets rigidly restricted in sodium. These patients particularly have been benefited by the use of resin. Some patients who faithfully adhere to strict low sodium diets, may receive added benefit from the additional sodium restriction afforded by the resin.

Resin therapy has been found especially useful in patients in whom mercurial diuretics have not been effective in promoting diuresis. It has been noted by several observers that the ammonium form of resin potentiates the action of mercurial diuretics. The mechanism for this potentiation remains unknown.

In conclusion, it is important to state that the cation exchange resins are not a cure-all, and not a complete solution for the dietary management of congestive heart failure or edematous patients. Furthermore, resins are not indicated in all patients with heart failure. Most patients with congestive heart failure respond to rest, digitalis, and moderate restriction of their sodium intake and will remain com-

pensated for months or even years under such a regime.

SUMMARY

Cation exchange resins are insoluble, organic compounds arranged in a structure that resembles a crystal lattice. Each structural element has the capacity of removing one type of ion from solution in exchange for another. Factors which control the efficiency or exchange potential of a resin include pore size of the molecular lattice, size of the resin particle, concentration of the resin in solution, nature of the functional group, size of the cation in solution, the valence and atomic weight of the cation, and the pH of the solution. The precise limits of the exchange capacity of a resin within the environment of the gut lumen have yet to be determined. The three main types of resins as determined by the functional group are the sulfonic acid, the carboxylic acid, and the phenolic acid exchangers. The commercial preparations are all of the carboxylic type and are partially in the potassium cycle.

The significance of renal factors in the pathogenesis of congestive heart failure has been emphasized. An expansion of the extracellular fluid compartment of significant degree, as found in cardiac edema,

results from sodium retention by the kidney. Sodium has an inherent priority over water in the production of edema because the amount of water reabsorbed is directly proportional to the amount of osmotically active solute (sodium and associated anions) reabsorbed. Control of sodium reabsorption by the renal tubule is mediated primarily through the secretions of the adrenal cortical hormone. Although there is much evidence for increased adrenal cortical activity in congestive heart failure, the specific mechanisms involved in the stimulus of the hormone remain obscure.

The recognition of the importance of sodium restriction in the treatment of cardiac edema constitutes a significant advance in medical progress. Sodium is the main factor in the osmotic regulation of the extracellular fluid and reduction of its concentration is followed by excretion of water as the kidney attempts to maintain normal osmotic relationships. Increased output of water is followed by a reduction of the volume of the blood and tissue fluids. The use of cation exchange resins results in the removal of sodium through the gastro-intestinal tract and thus, theoretically, produces a diuresis similar to that produced by sodium restriction. Numerous electrolyte studies during the use

of resins, both in animals and in human subjects, have been reported in the literature. Most investigators observed increased fecal excretion of sodium, potassium, and calcium, mild to moderate acidosis, decreased serum potassium levels, increased serum chloride levels, normal to decreased serum sodium levels, and normal serum calcium levels.

Many complications of resin therapy have been reported. Metabolic acidosis occurs frequently but is usually not severe. Administration of a resin partially in the potassium cycle helps to prevent this complication. Hypokalemia, formerly a common complication, now can be prevented by use of the potassium-cycle resin. Sodium depletion is an infrequent but dangerous hazard of resin therapy and its possibility must always be kept in mind. Calcium depletion is a complication occurring only during prolonged resin therapy and can be prevented by administering calcium supplements. No clinical evidence of deficiencies of other electrolytes, iron, vitamins, or amino acids has been reported. Urinary casts appear only as an incidental finding during resin administration. Impalatability of resins and gastro-intestinal disturbances resulting from resin administration are important practical complications and limit, to some extent, the use of resins.

A review of the literature on the use of resins in congestive heart failure revealed that a large percentage of patients able to take the resin showed definite clinical improvement. These patients were benefited to the extent that symptoms of congestive failure were diminished, the necessity for mercurial injections was reduced, salt restriction was reduced, and the action of mercurial diuretics was potentiated.

The best tolerated and most effective dosage of resin is 15 grams after each meal.. The most satisfactory method of administration is an intermittent schedule of 4 days on the resin and 3 days off.

Resin therapy is contraindicated in patients with renal impairment of an appreciable degree, in patients who are not eating well, and in patients who manifest signs of the low salt syndrome.

Resin therapy is specifically indicated in patients with long standing congestive failure refractory to the conventional methods of treatment, in patients who are unable to adhere to a low sodium diet or unable to reach a suitable level of sodium restriction, and in patients in whom mercurial diuretics will not promote diuresis.

CONCLUSIONS

The following statements briefly summarize the conclusions as expressed in previous sections of this paper and serve to re-emphasize their importance:

(a) Cation exchange resins are not a cure-all for patients in congestive failure.

(b) Resin administration is not a complete solution of the dietary management of cardiac edema.

(c) Resins are not indicated in all patients in congestive failure.

(d) Resin therapy can be used beneficially in selected patients with cardiac edema.

There is a distinct possibility that in the near future the synthesis of more efficient and more specific resins will expand their use in the treatment of congestive heart failure and in other clinical conditions.

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Royal F. Jester, Jr.

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