ION EXCHANGE RESINS IN CLINICAL MEDICINE

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To appreciate the use and the limitation of ion exchange resins it is necessary first to consider their mode of action[1]. The cation exchange resins are the most used in clinical medicine, and of these, there are two main types in general use—a sulphonated resin and a carboxylic resin. The latter is the more weakly acidic and the less effective on the acid side of neutrality but the more active weight for weight at optimal reaction. In practice, when used at the reaction of the alimentary tract, there is no material difference in their general action. Both resins have the same physico-chemical reactions. Their acidic nature enables them to bind loosely a series of cations. In weak solution—about M/100 cations with a higher valency are more firmly bound than those with lower valency and ions of equal valency are bound more firmly the higher their place in the periodic table.

In stronger solutions, the law of mass action applies however, and if the medium contains both sodium and potassium in amounts over M/10, then the resin will be found to bind sodium as well as potassium. With excess of sodium the resin will absorb more sodium than potassium. The rate at which these exchanges take place varies with the concentration of cations, size of resin particle and degree of mixing. With particles of size 50 to 100 μ, such as are used in pharmaceutical preparations, with constant mixing and cation concentration about that found in the gut, equilibrium can be established in about ten minutes in *in vitro* experiments.

In the human alimentary canal, the composition of the fluid surrounding the resin will vary with its progress through the gut. Initially, the composition will be largely determined by the food, but the dilution of the bolus in the upper alimentary tract with digestive juices containing a high proportion of sodium will cause the resin to take up sodium in excess of potassium. In the colon, the fluid excreted contains much more potassium and so the resin will relinquish its sodium in favour of potassium, and also of calcium and magnesium.

These effects have been well shown by Spencer, Ross and Lloyd-Thomas[2]. They also demonstrated the effect of aperients which decrease the time of stay of the resin in the large gut and showed that the amount of displacement of sodium by potassium increased with the delay in the colon, and that the result of giving aperients was therefore, to increase the amount of sodium and decrease the amount of potassium combining with the resin. However, their figures show some increased loss of potassium in the stool as a result of the aperient.

The amount of calcium and magnesium taken up by the resin will be greater as the relative amount of sodium and potassium in the fluid lessens with passage down the colon. As only ionic concentration is concerned in ion exchange, the bulk of the calcium and magnesium will

not enter into the exchange, owing to their being present in an insoluble form. Also the amount of calcium excreted in the digestive juices must be very small.

Resins can be used in several forms, combined with hydrogen, ammonium, potassium or sodium. The hydrogen form will readily exchange its H for sodium or potassium, thus freeing a H ion with which the body will have to deal and being acidic it may cause ulceration of the mouth.

TABLE I

DAILY EXCRETION OF CATIONS IN THE STOOLS

	Total (m.Eq)		Bound to Resin (m.Eq/g.)		
	Na	K	Na	K	Na/K
Resin only	21 (13–37)	69 (58–106)	0·32	1·2	0·26
Resin and purge	63 (39–114)	103 (73–127)	0·68	0·93	0·73

Taken from a paper by Spencer, Ross and Lloyd-Thomas, *British Medical Journal*, 1954, 1, 603.

The ammonium form is neutral but although causing no trouble when taken by mouth, ammonium is exchanged for sodium and potassium, the product when metabolised by the liver, also produces an acid ion. Both these resins are therefore, liable to produce an acidosis. The potassium form will exchange its potassium for sodium, but the amount of sodium ultimately bound to resin will not be great as the potassium ions of the resin will increase the proportion of potassium to sodium present in the surrounding fluid. In the same way, the sodium form will exchange with potassium. Neither the potassium or sodium forms will disturb the acid base balance but both will exchange with calcium and magnesium.

Resins are used mostly in conditions in which there is retention of sodium and water, such as cardiac failure, renal disease (nephrotic syndrome) toxæmia of pregnancy and cirrhosis of the liver. They are also used in hypertension.

The homeostatic control of the extracellular fluid space is a complex one[3,4], involving the maintenance at optimum level of the osmotic and oncotic pressures of the plasma, the correct adjustment of the glomerular filtration rate, the consumption of adequate salt and water, and a normal adrenocortical function. If this is carried out normally, the total body sodium will be kept at a constant level. The distribution of the extracellular fluid between plasma and interstitial fluid will depend on the plasma proteins and the capillary pressure, and the even distribution between various parts of the body depends on the normality of the circulation and muscle tone. Resins can thus be really effective only if the remaining mechanisms are capable of functioning at a reasonable degree of efficiency.

In general, œdema indicates the presence of excess sodium in the body. Dietary restriction of sodium to less than 0·5 g. per day is difficult, Carey[5] states that 2 g. of sodium chloride (0·8 g. of sodium) per day is the lowest the diet can be reduced to without being rendered completely unpalatable. As there is obligatory loss of sodium, both in urine and

sweat, restriction of sodium intake to this level will prevent an accumulation of more sodium in the body, and if steps are taken to increase the sodium loss by sweating and a high fluid intake, a slow loss of sodium to the body can be produced. It is not possible to cause a rapid loss of sodium at all easily by dietary restrictions alone.

Ion exchange resins will remove sodium from the body and reduce the excess sodium load, providing the remaining mechanisms are functioning adequately. This will in turn get rid of the œdema. The underlying pathological condition will not be affected, although removal of the mechanical effects of fluid retention will often allow embarrassed mechanisms to function better.

The fundamental action of resins as a sodium remover are similar in all the clinical conditions for which they are used, except in hypertension without obvious œdema. In this condition it is claimed that a low sodium diet is often effective in reducing the blood pressure and resins have been used as a reinforcement of a low sodium diet[6], or to enable some salt to be taken safely in the diet. In the absence of œdema it is unwise to remove sodium from the body but it may well be that by reducing the sodium to be excreted by the kidney, there will be some beneficial readjustment of the kidney's pressure needs for filtration. However, the clinical reports of the usefulness of resins in hypertension, are in general, not very optimistic[7].

Many authors have noted that resins can be used with advantage in conjunction with mercurial diuretics[8,9]. After a time, many patients become resistant to mercurial diuretics and Schwartz and Relman[10,11] explained this by showing that the prolonged effect of mercurial diuretics produced hypochloræmic alkalosis. If this became marked, the diuretic effect of the mercurials ceased. As the effect of resins is usually to cause an acidosis, it can be easily seen how the combination of resins and mercurials will mutually aid each other's action.

In cardiac failure, resin treatment has a definite place[12,13]. When prolonged treatment has to be undertaken intermittent use of resins is to be preferred, periods of about six months appear to be satisfactory, but after that, many people record less gratifying results[7] owing to the side effects, especially possible loss of calcium. In the same way, regular treatment with mercurial diuretics may be found to be unsatisfactory over prolonged periods. The intermittent treatment gives the opportunity to replenish depleted calcium stores and quite likely also other unrecognised depletions, such as iron.

If the patient is being treated with digitalis, the serum potassium level must be watched, since with lower potassium levels, the action of the digitalis becomes more marked[14]. It is wiser to reduce the digitalis in advance and only increase it when a state of electrolyte equilibrium has been established.

When ascites or hydrothorax complicate the œdema, resins are less effective, and removal of the fluids by puncture is recommended. If the fluid accumulated only because of the tissue œdema, it should not return if the resin is controlling the œdema.

The long term use of resins calls for careful attention. The amount of sodium removed by the resin, together with the loss in sweat and urine, will exceed the sodium in the diet if a low sodium diet is given. This will cause a reduction of the extracellular fluid below the optimum level and frequently instead of this happening the percentage of sodium in the fluid will fall to below the normal value and symptoms of sodium lack will occur, such as marked lassitude, loss of appetite, vomiting, and a rising blood urea and blood pressure, which may mimic uræmia.

This low salt syndrome[15] occurs in two forms. It can occur more or less spontaneously, in which case it has a very bad prognosis, and attempts at replacing the sodium by giving salt in the diet will merely result in increased œdema without improving the lot of the patient. If, on the other hand, it is the result of active therapeutic measures, such as mercurials or resins, then an adequate amount of hypertonic saline will rapidly remove the symptoms and quite often results in a loss of the œdema.

To be worth using, a treatment which needs constant watching should be more effective than other less troublesome methods. In nephrotic œdema in children this is by no means the case as often loss of renal function is sufficient to prevent the use of resins and even when these are initially successful, the œdema will return, but with a low serum sodium which prevents their further use[16]. In the adult variety of nephroic œdema, which often behaves differently to that of children, the recorded results of resin treatment are less gloomy[17].

In both hypertension and nephrotic œdema, the kidney function may be impaired and the prolonged use of resins in the ammonium cycle—the most effective form—will cause a progressive acidosis owing to the kidney being unable to bring into action the various base saving mechanisms. In nephrosis in particular, the damaged kidney may be unable to maintain the normal plasma osmotic pressure and when the excess sodium is removed by the resin (or even by prolonged low sodium diet), the water in which it was dissolved remains in the body and no reduction of œdema occurs. As a result the sodium may fall to a dangerously low level. A similar renal failure may also occur during the course of an apparently successful treatment, and this will be shown by an increase in œdema (or in weight) with no obvious cause. It is therefore essential in all long-term treatments for frequent blood electrolyte studies to be made.

Another complication of using the hydrogen or ammonium cycle resins alone, is the removal of potassium from the body which would cause hypokalæmic symptoms (cardiac failure, abdominal distension and œdema, etc.) to appear. This is avoided by using a mixture of the ammonium and potassium resins, but it is by no means certain that an optimum mixture is being used in every case. Close attention must be given to the plasma potassium level, not only to prevent hypokalæmia but also hyperkalæmia, since with damaged renal function this state has been found when the standard mixture of ammonium and potassium resins were employed.

A further complication sometimes recorded is tetany. Since so little calcium is removed that most balance studies fail to show a negative

balance[15], and as there is so much calcium available in the bones, it seems unlikely that resins alone could account for the low serum calcium. It is well recognised that the blood calcium is maintained at a very constant level irrespective of any dietetic measures, its level being set apparently by the activity of the parathyroid gland. There is very considerable variation in the literature on the effect of resins on the calcium level in the blood[5,6]. Many record constantly normal results and state that they have observed no clinical manifestations on prolonged use of resins. Others report occasional tetany[18], and many more record slight lowering of the calcium in the blood, but very rarely levels below 8 mg. per 100 ml. It is unlikely that symptoms of tetany will occur with a calcium no lower than this. On the other hand, for example in nephrosis, spontaneous tetany is known to occur quite apart from the use of resins.

In cirrhosis of the liver, treatment has a peculiar danger if resin in the ammonium form is used[9]. If there is much liver damage, the ammonium liberated will not be metabolised to urea and severe toxic symptoms may occur due to raised blood ammonia. If the liver function is good however, resin treatment can be successful[13,19].

Good results have been claimed in early toxæmia of pregnancy[5,20], and as there is no question of a chronic long-term treatment, it would seem a reasonable form of treatment.

Another use of resins is in acute renal failure. While it is possible by dietetic measures to minimise the rise of the blood urea, the development of acidosis and the occurrence of œdema, it is impossible to control the steady rise of serum potassium, which may indeed be the final cause of death. Resins in the sodium form can be used with marked success[21,22] in particular, as the amount of potassium to be removed is not very great; the loss of one gram in an average adult would reduce the blood level by about 7 mg., this would only need about 20 to 30 gm. of resin. A similar use may occur occasionally in the treatment of acute adrenocortical failure when the serum potassium may rise to very high levels.

While the cation binding resins are the most used, the anion binding resins formed by using amino-acid groups instead of the sulphonic or carboxyl groups have also some clinical application. In an endeavour to counteract the acidosis caused by the hydrogen or ammonium resin, anion binding resins have been added to the mixture. This will increase the bulk of the resins needed to bind a given amount of sodium and in practice has not been very successful[23].

Anion binding resins have also been tried as an antacid in gastric ulcer treatment. It shares with several other insoluble acid bonding substances the advantage that any unused excess will not be absorbed and so increase the alkalosis which inevitably results from the removal of large amounts of free hydrochloric acid from the body. Segal *et al*[24], in a paper reviewing the results of using resins in ulcer treatment, record a reasonably successful result in about 65 per cent. of the cases, using a dose of approximately 2 g. of resin every two hours. They found no side effects from this treatment, and in particular, had no trouble with constipation.

It is rather difficult to assess the real place of resins in therapy. They are of great value in hyperkalaemic states and a supply of the sodium form should be available in all hospitals to treat acute cases. For all other conditions, as good or better methods of treatment are available which do not call for so much clinical chemistry. For those who find a low salt diet both advantageous and intolerable, resins will give some slight lightening of their dietetic burden. In most cases however, the main usefulness of resins will be as an adjuvant or a temporary alternative to mercurial or other diuretics, or to low salt diets.

Resins can be of value as alternative methods of treatment over short periods and some patients will prefer to use resins rather than have periodic injections of mercurial diuretics. Others, however, find the taking of the large amount of resin so unpleasant, that they do not tolerate the treatment for prolonged periods.

The complication of severe constipation and even of semi-obstruction, adds one more difficulty in their use, but there is no doubt that there is a definite place in therapeutics for the ion exchange resins.

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