# Ion Exchange and Adsorption Agents in Medicine

*The Concept of Intestinal Bionomics*

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*Illustrated with 15 line drawings and 11 photographs*

1955

# Foreword

In the early part of 1944, I began the investigation of ion exchange resins for medical use. The first result of that effort was the application of the anion exchangers in the treatment of peptic ulcer; the second was the use of cation exchangers for sodium reduction. Since the launching of these two resin types for general clinical use, a broader and greater sphere of application has arisen, that of conditioning of the gastrointestinal tract. By conditioning, I mean to suggest a state in which toxic chemicals are retained in the intestine and beneficial and nutrient materials permitted entrance into the system. This could well be defined as differential or selective ion exchange and adsorption for medical purposes.

It is my contention, as yet unsubstantiated by clinical observations, that all chronic degenerative disease has as an important component in its etiology the absorption from the intestine of small quantities of toxic chemicals. These agents produce imperceptible but irreversible changes in tissues and in the course of years create gross pathology. I believe that the absorption of these toxic agents can be prevented by proper selection of ion exchange and adsorption materials. As a first effort in substantiation of my major theme, I offer the material of this volume.

Of the many persons who have been of help in the preparation, proofreading and typing of the manuscript, my special thanks are due Henry Hopkins, M.D., who reviewed and corrected the clinical sections of the volume.

GUSTAV J. MARTIN

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# Contents

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*CHAPTER 1*

# Ions and Solutions



## IONIZATION, GENERAL

TO UNDERSTAND ion exchange materials is to understand the nature of ions and their behavior in solution. The logical introduction to the field is therefore a brief review of the physical chemistry of ionization. Throughout this summary, it should be held in mind that the behavior of the ion-active groups of insoluble exchangers is identical with that of those same groups attached to soluble molecular units. The simplicity and the complexity of each system are reflected in the other.

The number $6.02 \times 10^{23}$ is a fundamental constant in physical chemistry, called Avogadro's number. It represents the number of molecules in a gram molecule of any given chemical. A gram molecule is in turn that molecular weight of a given substance expressed in grams; thus, the gram molecular weight of sodium chloride is 58.5, and this weight of sodium chloride would contain $6.02 \times 10^{23}$ individual molecules of salt.

Avogadro offered the hypothesis that the physical behavior of substances would represent a function of the number of particles involved. Actual measurements of systems such as those of salts in solution showed marked discrepancies from the hypothesis and led van't Hoff to point out the distinctions between solutions of materials like cane sugar, which behaved according to the hypothesis, and solutions of substances like salts, acids and bases, which did not. It remained for Arrhenius (1887) to propose the theory of electrolytic dissociation,

which accounted for the abnormal osmotic pressures exerted by solutions of acids, bases and salts. According to this concept, aqueous solutions of acids, bases and salts dissociate into positively and negatively charged particles or ions. The dissociation increases the number of particles in solutions, bringing the behavior of such systems within the scope of Avogadro's hypothesis. Dissociations occur as follows:

$$HCl \rightleftarrows H^+ + Cl^-$$
$$HC_2H_3O_2 \rightleftarrows H^+ + C_2H_3O_2^-$$
$$NH_4OH \rightleftarrows NH_4^+ + OH^-$$
$$NaCl \rightleftarrows Na^+ + Cl^-$$

These equations indicate the dissociation of an acid such as hydrochloric acid into hydrogen and chloride ions; they also indicate the reassociation of these ions into the molecular form of the acid. An equilibrium is established which can be expressed as an equilibrium constant:

$$K = \frac{(H^+)(Cl^-)}{(HCl)}$$

The degree of dissociation of a given electrolyte is a function of its concentration; the more dilute the solution, the greater is the degree of dissociation. At any finite concentration, there are always some undissociated molecules.

Completion of the picture of ionization requires extension of the above concepts, which may tend to confuse, but such extension is essential in the interests of accuracy. With certain strong electrolytes like sodium or potassium chloride, electrical conductance measurements and osmotic phenomena indicate divergence from the electrolytic dissociation concept, and these divergences are clarified by x-ray analysis showing the existence of a completely ionic state even in crystal form. For example, the crystal lattice of potassium chloride exists in the form of ions. For these strong electrolytes, the concept of degree of dissociation loses its significance because complete ionization exists.

However, if complete ionization existed, the properties of salts and strong acids and bases in solutions would be a function of the total number of ions possible, e.g., two for sodium chloride, three for potassium sulfate, four for potassium ferricyanide. This assumption was not in accord with experimental findings and led directly to the formulation of the interionic attraction theory of Debye and Hückel (1923*a, b*). This concept points out that oppositely charged ions attract each other and that this attraction causes deviation from the behavior of ideal

solutions. The degree and extent of the interionic attraction varies with concentration and for all practical purposes vanishes in extremely dilute solutions.

The ionization concept came full circle with the introduction of the theory of ionic strength by Lewis and Randall (1923). Ionic strength may be regarded as the effective ionic activity of a given electrolyte. It is a function of valence and is calculated by multiplying the concentration of each ion by the square of its valence, adding all these quantities together and dividing by a factor of two. The introduction of the ionic strength factor into equations dealing with ionic behavior brings into line all deviations from such equations caused by the use of the theoretical ionic concentration factors.

Two types of chemical bonds are generally recognized, the covalent and the ionic. With the covalent type, the over-all structure is established by the sharing of electrons. This is characteristic of the carbon-carbon and the carbon-hydrogen bonds. Ionization is impossible. The ionic type of bond results from actual electron transfer from one atom to another. Such transfer occurs with any electrolyte. For example, the ion formation with potassium bromide results from the transfer of an electron from the potassium to the bromine, and the consequent greater stability of the outer electron shells of each unit. The electron transfer produces the ion, and the interionic attractive forces are due to the respective loss and gain of a single electron. The tendency of all atomic forms is to assume a state corresponding most closely to that of inert and nonreactive rare gases, helium, argon, neon and xenon. They will form anions or cations, respectively, as the gain or loss of an electron tends to confer greater stability in the outer electron shell.

In any consideration of ionization phenomena as applied to biological systems, the formation of various types of complex ions must be considered. The following examples serve to illustrate this point:

$$H_2SO_4 \rightleftarrows H^+ + HSO_4^-$$
$$BaCl_2 \rightleftarrows BaCl^+ + Cl^-$$

Ionization phenomena in a system consisting only of water and phosphoric acid result in the formation of four types of ions, as follows:

$$H_3PO_4 \rightleftarrows H^+ + H_2PO_4^- \rightleftarrows H^+ + HPO_4^{---}$$
$$\downarrow \quad \uparrow$$
$$H^+ + PO_4^{---}$$

From a consideration of this comparatively simple system, the magnitude of the complexities of ionization in a living milieu is enormous.

Another type of complex ion formation follows the interaction of potassium cyanide and silver nitrate:

$$2KCN + AgNO_3 \rightarrow KNO_3 + KAg(CN)_2$$

The complex so formed dissociates as follows:

$$KAg(CN)_2 \rightleftarrows K^+ + Ag(CN)_2^-$$

As indicated by Bull (1951), two major factors govern the existence of ions in solution. The first of these is the attraction of ions for each other, which is proportional to the charge on each ion, the distance of the ions from each other, and the dielectric constant of the solvent. In biological systems, the solvent is water with a constant of 78.54 at 25° C., indicating that water decreases the affinity between ions to 1/78 of that exerted in crystal form. The second factor is ionic hydration, and this will vary in biological systems much as it does in simpler isolated inorganic combinations. Solutes, whether electrolytes or not, form hydrates or solvates in water solution. Whenever a hydrate is formed, the ion plus the water forms a molecular complex acting as a single dissolved unit. The water used up in forming the hydrate is thus withdrawn from the pool of solvent. This factor of ionic hydration is of marked significance in the behavior of ion exchangers.

Some idea of the differences in ionic radii is obtained from the figures of Pauling (1940), given in angstrom units; $Li^+$, 0.60; $Na^+$, 0.95; $K^+$, 1.33; $Mg^{++}$, 0.65; $Ca^{++}$, 0.99; $Cl^-$, 1.81; $I^-$, 2.16; $SO_4^=$, 1.51. Those ions in a given valence series will hydrate to a greater degree as their ionic radii decrease (Bull, 1951); however, the effective number of water molecules associated with anions increases with increasing radii of the anions involved (Stokes and Robinson, 1948).

Ionic hydration is the phenomenon underlying the lyotropic or Hofmeister series, listing relative powers of anion and cation to affect an entire host of biological and physical properties of proteins, colloids, etc. It is perhaps at this point that the extent and degree of ion exchange in biological systems becomes most apparent. Studies of ion exchange resins and similar materials reveal the similarities of their behavior with proteins and other materials in biological systems. This entire scheme of behavior rests in large measure upon ionic hydration. The Hofmeister series for cations is:

$$Th > Al > H > Ba > Sr > Ca > K > Na > Li$$

and for anions:

$$Citrate > Tartrate > SO_4 > Acetate > Cl > NO_3 > Br > I > CNS$$

## HYDROGEN IONS, ACIDS AND BASES

In general, the term hydrogen ion concentration refers in fact to the hydrogen ion activity or the apparent hydrogen ion concentration. All physical and chemical methods of measurement give a value corresponding to the hydrogen ion activity.

In recent years, many new concepts have appeared in studies of hydrogen ions. One of these involves the fact of hydration of the hydrogen ion with the formation of hydronium ions. The degree of hydration may progress and an entire series of higher polymers be formed (Huggins, 1936*a*, *b*), thus:

$$H^+ + H_2O \rightleftarrows H_3O^+ + H_2O \rightleftarrows H_5O_2^+ + H_2O \rightleftarrows H_7O_3^+$$

In this and all other systems, the hydrogen ion can be regarded as a proton, infinitely small in size, and capable of penetrating any molecule with which it comes in contact.

Another accepted innovation of the time-honored ionization concept concerns the theory of Brönsted (1923, 1928) and Lowry (1923), who define an acid as any substance capable of yielding protons, and a base as any substance able to accept a proton. The concept is expressed in the following equation:

$$A \rightleftarrows H^+ + B$$

where A is an acid and B is a base. From this it can be stated that the reactions of acids and bases need not necessarily involve the elements of water. Bull (1951) gives as an example of this the reaction of sodium acetate and hydrochloric acid, as follows:

$$CH_3COONa + HCl \rightarrow CH_3COOH + NaCl$$

An acid, HA, will dissociate, forming $H^+$ and $A^-$, as expressed by

$$HA \rightleftarrows H^+ + A^-$$

Applying the law of mass action to this system and expressing the concentrations of hydrogen ions and acid anions, we form the equation

$$K_a = \frac{(H^+)(A^-)}{(HA)}$$

which involves the acid dissociation constant, $K_a$. The above equation states that the product of the concentration of hydrogen ions and the anions from the acid, divided by the concentration of the undissociated acid, is in fact a constant. The magnitude of the constant determines

the strength of the acid. If the acid is strong the constant is large, as more dissociation has occurred; if the acid is weak the constant is small, indicating a greater concentration of the acid in the undissociated form. In general, interest is centered in the so-called weak acids and bases, which are not completely dissociated. Consideration of the weak base leads to formulations corresponding to those for the acids:

$$BOH \rightleftarrows B^+ + OH^-$$

Applying the law of mass action to this system, we arrive at the formulation of an equation for the determination of the base dissociation constant:

$$K_b = \frac{(B^+)(OH^-)}{(BOH)}$$

As with the acids, there are weak bases and strong bases: those which dissociate very little and those which dissociate almost 100 per cent or are, in fact, in ionic form prior to solution.

In any consideration of the behavior of weak acids and bases in solution, the factor of the ionization of water must be known. Water dissociates into hydrogen and hydroxyl ions:

$$H_2O \rightleftarrows H^+ + OH^-$$

and this dissociation can be expressed as follows:

$$K_{H_2O} = \frac{(H^+)(OH^-)}{(H_2O)}$$

The value of the water dissociation constant is for a temperature of 25° C., $1.008 \times 10^{-14}$. The factor for water in the above equation is constant, and therefore the dissociation constant for water represents, in fact, the product of the concentration or activities of hydroxyl and hydrogen ions expressed in gram equivalent weights. The dissociation constant of water is an extremely important factor in biological systems, as it automatically implies that regardless of other components of a given system, the product of hydrogen and hydroxyl ion concentrations must be $10^{-14}$. If the system is alkaline, there will be a correspondingly low concentration of hydrogen ions, and vice versa.

The equation given above representing the acid dissociation constant can be written as follows:

$$\frac{1}{(H^+)} = \frac{(A^-)}{K_a(HA)}$$

Further modification of this equation may be made by taking the

logarithm of both sides of the equation and expressing it as follows:

$$\log \frac{1}{(H^+)} = \log \frac{1}{K_a} + \log \frac{(A^-)}{(HA)}$$

The logarithm of the reciprocal of the hydrogen ion concentration as expressed above is called pH.

Acetic acid can be used as an example of a weak acid with biological significance. It has a dissociation constant $K_a$ at 25° C. of roughly $10^{-5}$. Such constants are frequently expressed in terms similar to that of pH and designated as $pK_a$. The latter expression is the logarithm of the reciprocal of the dissociation constant, $K_a$. The $pK_a$ of acetic acid would be roughly 5. Lactic acid has a dissociation constant $K_a$ of approximately $10^{-4}$ at the above temperature, giving it a $pK_a$ of 4. This means that lactic acid is a stronger acid than is acetic. The smaller the $pK_a$ value, the stronger the acid; the smaller the dissociation constant, the weaker the acid.

Hydrogen ion concentrations can be determined by the indicator method or by the electrometric method. The indicator method depends upon the variation in color assumed by various organic substances with shift in pH. The electrometric method depends upon the electromotive force of a cell whose potential is a direct function of the hydrogen ion concentration.

In dealing with pH values it is good to remember that the scale is not arithmetic, i.e., when a solution is brought from pH 7 to pH 6, the arithmetical increase in hydrogen ion activity is only one-tenth of the increase in going from pH 6 to pH 5 (Bull, 1951).

Biological systems are generally buffered. The term buffer is applied to a substance which tends to resist changes in pH and to increase the amount of acid or alkali needed to cause a unit change in pH. The best buffers are mixtures of weak acids or bases with their corresponding salts. For example, if one adds hydrochloric acid of pH 1.0 to a solution of 0.3 N trisodium phosphate, the following reactions will occur:

$$Na_3PO_4 + HCl \rightarrow NaCl + Na_2HPO_4 \quad (1)$$
$$Na_2HPO_4 + HCl \rightarrow NaCl + NaH_2PO_4 \quad (2)$$
$$NaH_2PO_4 + HCl \rightarrow NaCl + H_3PO_4 \quad (3)$$

The pH of a system in reaction 1 is about 9.0; in reaction 2 about 4.5; and in reaction 3 about 2.5. This means that three equivalents of hydrochloric acid of pH 1.0 have been needed to shift the pH of the sodium phosphate from 10.5 to 2.5.

In a similar manner, the salt of a weak acid can react with a strong acid and prevent the pH from shifting to the degree normally expected:

$$Na_2CO_3 + HCl \rightarrow NaCl + NaHCO_3$$
$$NaHCO_3 + HCl \rightarrow NaCl + H_2CO_3$$

As strong acids are buffered by the salts of weak acids, so strong bases are buffered by the salts of weak bases:

$$NH_4C_2H_3O_2 + NaOH \rightarrow NaC_2H_3O_2 + NH_4OH$$
$$NaH_2PO_4 + NaOH \rightarrow Na_2HPO_4 + H_2O$$

The importance of an understanding of the behavior of weak acids and bases lies in the fact that the cation and anion exchangers currently in use in medical practice are respectively a weak-acid cation exchanger and a weak-base anion exchanger. The effect of pH change on weak-acid and weak-base exchangers is much greater than it is on strong-acid or strong-base exchangers.

## BIOLOGICAL ION CONCENTRATIONS

Paleochemistry establishes the probable marine origin of the vertebrate by demonstrating the similarity in ionic composition of sea water and blood. The element magnesium is the only one which is dispro-

**TABLE**
**Ionic Composition of**

| *Ion* | *Blood* | | *Gastric juice* | | *Bile* | |
|---|---|---|---|---|---|---|
| | *Mg. %* | *MEq./l.* | *Mg. %* | *MEq./l.* | *Mg. %* | *MEq./l.* |
| Potassium | 16–22 | 4.1–5.6 | 40 | 10 | 10–47 | 2.6–12 |
| Sodium | 330 | 143 | 115 | 50 | 326–354 | 142–154 |
| Calcium | 9.0–11.5 | 4.5–5.8 | 4.1–8.6 | 2.0–4.3 | 4–9 | 2–4.5 |
| Magnesium | 1–3 | 0.83–2.5 | 2.2–9.4 | 1.8–7.8 | 1.82 | 1.5 |
| Chloride | 370 | 100 | 500 | 141 | 320–355 | 90–100 |
| Sulfate | 19 | 4.0 | Trace | — | 0.3 | 0.06 |
| Phosphate | 10 | 3.1 | 1.1–4.2 | 0.34–1.3 | 12.5 | 7.3 |
| Bicarbonate | 164 | 27 | 0–130 | 0–21 | 244 | 40 |
| pH | 7.3–7.4 | | 1.2–1.8 | | 7.4–8.5 | |
| Titratable acidity or alkalinity | — | 146.6 | — | 123.3 | — | 151–181 |

portionately high in sea water (Macallum, 1926). For general orientation on ionic composition, the blood serum of mammals can be regarded as slightly diluted sea water. A further extension of this generalization is that of regarding the other body fluids as modified blood serum. This concept permits an immediate basis for consideration of the effect of ion exchange resins on blood fluids. As this monograph deals with the gastrointestinal tract primarily, Table 1 is offered, giving ionic composition of sea water, blood, gastric juice, bile, pancreatic juice, small intestinal content, and large intestinal content.

In general, ion exchange resins functioning in an *in vitro* system of comparable ionic composition will behave as they do *in vivo;* however, the complexity of biological fluids is tremendous, and each organic moiety present may modify the ionic behavior of the fluid as well as the exchange function of the resin. *In vitro* studies of ion exchange must therefore be conducted with the milieu comparable in all respects to that found *in vivo*. In the final analysis, the biological fluid itself must form the milieu for study. Frequently, introductory examinations of exchangers can be conducted with artificially prepared ionic compositions.

Obviously, dietary composition and habits will modify the ionic composition of the gastrointestinal tract; and this in turn must be correlated with exchanger function.

**Biological Fluids**

| *Pancreatic juice* | | *Small intestine* | | *Large intestine* | | *Sea water* | |
|---|---|---|---|---|---|---|---|
| *Mg. %* | *MEq./l.* | *Mg. %* | *MEq./l.* | *Mg. %* | *MEq./l.* | *Mg. %* | *MEq./l.* |
| 11.7–15.6 | 5–4 | 15.6–19.5 | 4–5 | 33.6 | 8.6 | 37.5–39.1 | 9.6–10 |
| 317 | 138 | 322 | 140 | 347 | 151 | 1012–1044 | 440–454 |
| 4.4–6.4 | 2.2–3.2 | 5.0–12.8 | 2.5–6.4 | 10.0 | 5.0 | 36–40.8 | 18–20.4 |
| 0.34 | 0.28 | 1.2–2.4 | 1–2 | 1.95 | 1.6 | 123–127 | 101–104.5 |
| 213–284 | 60–80 | 262–365 | 74–103 | 310 | 87.5 | 1810–1899 | 510–535 |
| 39.4 | 8.2 | Trace | — | Trace | — | 240–255 | 50–53.2 |
| 0.125 | 0.039 | 8.3–24.5 | 2.61–7.66 | 54.4 | 17 | 6.4 | 2.0 |
| 610 | 100 | 12–195 | 2–32 | 559 | 91.8 | 13.4 | 2.2 |
| 7.5–8.8 | | 6.16–7.31 | | 8.03 | | 8.0 | |
| — | 50–160 | — | 158.2 | — | 164.6 | — | 550 |

## BIOLOGICAL SIGNIFICANCE OF IONS

The blaze of glory surrounding miracle hormones, vitamins and drugs has dimmed in the minds of many the greater importance of the inorganic ion. The proposal has been made that any protein in the proper environment may assume the characteristics of an enzyme (Sevag, 1945, 1951) and that "the proper environment is doubtless ionic in character." The effect of ions on protein structures and the immediate antagonisms associated therewith form "the dynamic functional systems around which the complex concatenation of living matter is built" (Martin, 1951).

The balance mechanisms forming the antagonisms among ions are of far greater importance than the function of absolute concentrations. Before reviewing briefly this interionic antagonism concept, a summary of the biological significance of individual ions is in order. There can be no doubt that the animal organism is extremely sensitive to ionic content, a fact reflected in the narrow limits for concentration of any given ion in the blood. The factors of absorption, excretion and in some instances storage are functional in the maintenance of blood serum levels. Generally, blood concentrations of ions reflect the tissue concentrations, but in abnormal states this generalization does not apply.

As stated by Martin (1951), anions and cations and their combinations constitute about 1 per cent of the mass of the body. These ions exert a multiplicity of functional characteristics; they are components of enzyme structures and cofactors for enzymes; they control protoplasmic colloidal states, form structural components of the body, and so on.

The function of inorganic ions as components or cofactors of enzymes could hardly be materially modified by ion removal via exchange resins; however, the ratio of ionic concentrations could be materially modified, and it is known that this ratio is determinant in many enzymatic systems. For example, magnesium and calcium ions activate acetylcholinesterase, while potassium inhibits this enzyme (Mendel *et al.*, 1939). Direct antagonism occurs between calcium or magnesium on the one hand and potassium on the other. There are many other examples of ionic antagonism in enzyme systems, but for this brief summary one more will suffice. Northrop (1942), using eserinized brain slices, noted that the formation of acetylcholine was enhanced by potassium ions and inhibited by either calcium or magnesium ions. It seems entirely probable that enzymatic activity would

be modified by the restriction of ion intake through the use of exchange resins, assuming that the removal of ions was not such as to leave blood and tissue ratios of these ions unchanged. In other words, the exchangers would have to remove ions selectively and not in proportion to their concentrations in natural biological fluids.

Of considerable interest to the clinician using exchangers is the problem of possible modification of patient reaction to drugs. Whether or not this actually happens in practice is not yet known, but the probability is there. Certainly ionic ratios markedly modify the reaction of the body and of specific tissues to different drugs. Lowering the ratio of calcium to sodium lowers the sympathetic response (Gley, 1928). As an example of the alteration of tissue sensitivity by ions, von Pinter-Kovats (1928) reported that the vasoconstrictor response of the rabbit ear to epinephrine requires the presence of calcium but not potassium. Conversely, drugs may sensitize to ions, as in the case of the veratrum alkaloids, which sensitize tissues to the potassium ion (Goutier, 1950).

One of the earliest clinical states to be recognized as a deviation from the normal in electrolyte balance was tetany. This condition is a reflection of the marked sensitivity of the nervous system to a calcium deficiency. The neuromuscular transmission systems manifest a state of irritability resulting in twitchings and convulsions. In the element calcium and its physiological role we find a unique example of the complexity of the mechanism controlling ionic balance. The physiologically functional calcium of the blood stream is ionic. This is in contrast to the calcium found in this biological fluid in combination in colloidal salts of phosphate and citrate, and to that larger portion of the calcium bound in the form of nonionized and nondiffusible calcium-protein complex. The ionized calcium is controlled in large measure by the parathyroids. In addition to the role of the hormone in the modification of available calcium, vitamin D is involved via the absorption of calcium from the gastrointestinal tract. Limitation of hormonal and vitamin control of ionic calcium to the parathyroid hormone and to vitamin D would be the equivalent of examining but a small central portion of an extremely complex canvas. Almost all hormones and vitamins play some role in the control of electrolyte balance and specifically in the metabolism of calcium. Further, calcium function is correlated with that of phosphate and with virtually all other cations. One final point should be made relative to the role of the kidney; this organ controls in some measure both calcium and