

present. Percussion always gives a dull note on the affected side of the chest, both laterally and behind, the line of dullness being higher in front and lower in the back when the patient sits up, and reversed when the patient lies down.

In seventeen of the forty-seven cases chylothorax was accompanied by chylous ascites, and in one instance by chylopericardium. In one case there was chyluria, and in another milky diarrhoea.

The symptoms referable to other organs are usually due to the same pathological alterations as those which have brought about the chylothorax. In cases of external injury to the duct very few symptoms other than those mentioned appear.

DIAGNOSIS.—The only evidence upon which a positive diagnosis of chylothorax can be based is that afforded by an examination of the fluid. This fluid, as withdrawn by an aspirator, is usually semitranslucent, milky, and opalescent. Its specific gravity is 1.020 in most cases. If allowed to stand, the fluid separates into two layers, an upper, slightly more yellow in color, and resembling cream in consistence, and a lower one, watery in character. If the whole is well shaken and extracted with ether or treated with sodium or potassium hydrate, the fluid becomes clear and loses its milkiness. Chemical examination of the fluid shows that from ninety to ninety-nine per cent. is water. Of the solids, the fat varies from 0.02 to 0.92 per cent.; salts and albumins, and sometimes a small amount of sugar, forming the remainder.

PROGNOSIS.—In many cases the prognosis of chylothorax is good. In those which are due to obstruction, the anastomoses of the thoracic duct may do compensatory work, and thus the condition may be relieved. In cases due to injury to the duct from external causes, proper treatment frequently brings about a cure.

TREATMENT.—For those cases in which the chylothorax is due to some chronic obstruction, aspiration of the fluid, accompanied by rest and nourishing food, is about all that can be done. Cases due to injuries of the chest are treated in a similar manner.

In cases due to injury inflicted during an operation for the removal of carcinomatous or tuberculous lymph nodes in the neck, the duct may be ligated, resected, or packed, all of which procedures have been used.

Frederick A. Baldwin

Most of the literature of chylothorax is given by Bargebuhr, *Deutsches Archiv für klinische Medizin*, 1895, liv., 410, and by Shaw, *Journal of Pathology and Bacteriology*, 1900, vi., 330.

DISSOCIATION, DIFFUSION AND ACTION OF SALTS.—The advance of physical chemistry in the last fifteen years has thrown a new light upon the behavior of salts in the tissues, and promises to form the basis of the explanation of their presence in all forms of living matter, as well as of much of their therapeutic value. The chief phenomena bearing on biology and medicine are the dissociation of salts and their relation to diffusion and osmosis, and before the results of the application of physical-chemical methods to the biological sciences can be appreciated some knowledge of the recent advances in the theory of these phenomena is requisite.

Dissociation. Ions.—It was formerly held that common salt dissolved in water remained in the same form as that which is familiar in the dry state, the only difference being that crystals divided into molecules. It is now recognized, however, that not only are the molecules isolated from each other, but that a certain number of molecules undergo still further division. The products of this molecular division are known as *ions*, and in the case of common salt are Na ions and Cl ions. The amount of dissociation that occurs varies with the strength of the solution; the weaker the solution the greater the percentage of salt undergoing dissociation. In a one-per-cent. solution of sodium chloride only about one-fifth of the salt is present in the form of molecules, the rest having dissociated into the two ions. These ions are not to be confused with atoms, for although sodium and chloride ions are present, the solution of course possesses none of the

properties of metallic sodium or of free chlorine. The ions differ from the atoms in carrying a charge of electricity, the charge of the sodium ion being positive, while that of the chloride ion is negative.

If a battery be connected with the solution the sodium ions hurry to the negative pole or cathode, while the chloride ions give up their charge at the positive or anode. The sodium ion is therefore known as the *cation*, the chloride as the *anion*. At the moment at which the charge of an ion is given up the ion changes to an atom, but it immediately forms fresh combinations with the water, in the present instance NaOH and HCl.

Other salts undergo a similar dissociation in solution in water: KBr forms K and Br ions; NaNO₃, Na and NO₃ ions; K₂SO₄ divides into three ions, two potassium and one SO₄; ammonium oxalate forms two NH₄ ions and one oxalate anion, and so forth. The dissociation of acids and alkalis is of great importance, but resembles exactly that of the other salts, acids forming hydrogen cations and the rest of the molecule forming the anion, while alkalis divide into a hydroxyl anion and a metallic cation; HCl thus becomes hydrogen and chloride ions; NaHO, sodium and hydroxyl (HO) ions.

The ions in a solution are in constant motion, and the anions and cations of a substance in solution lose the connection which they possess in the solid state. Thus, when potassium bromide and sodium chloride are dissolved together in a sufficient amount of water, it is no longer correct to designate the result as a solution of potassium bromide and sodium chloride, for the potassium ions are in no closer connection with the bromide than with the chloride ions. The bodies present are really the potassium and sodium cations and the bromide and chloride anions. In the blood serum, for example, the phosphate ions present are not combined with the potassium nor the chloride with the sodium, but all four are independent, and it is incorrect to speak of the potassium phosphate of the blood serum. When a dilute solution of sodium hydrate is swallowed it is neutralized by the gastric juice, and the reaction is often stated as the formation of sodium chloride and water. In reality the hydrate solution contains sodium and hydroxyl ions, the gastric juice hydrogen and chloride ions, and the resultant fluid contains sodium and chloride ions. The change consists in the disappearance of the hydrogen and hydroxyl ions which have formed water, the chloride and sodium ions having been present to begin with and remaining unchanged.

Dissociation occurs in salts, including under this term acids and alkalis, but it is not developed equally in all salts. Those acids and bases which are generally considered to be the "stronger" dissociate more readily than the weaker combinations, and the monovalent salts more readily than the bivalent. The inorganic salts dissociate more readily than the organic, and the same holds true for the bases. All of those bodies in solution serve as electrical conductors; in fact, the passage of electricity through watery solutions is only possible through the presence of ions, and the conductivity of solutions is thus a measure of the degree of dissociation. Those substances which are dissociable are therefore known as electrolytes. On the other hand, many organic substances are incapable of conducting electricity and are also incapable of dissociation. Thus alcohol contains an hydroxyl (—OH) in combination with ethyl (C₂H₅), as sodium hydrate contains an hydroxyl in combination with sodium. Alcohol is, however, incapable of forming ions, and therefore is a non-electrolyte in aqueous solution, while sodium hydrate dissociates readily into hydroxyl and sodium ions, and these are capable of conveying an electric current.

Sodium hydrate has a characteristic action in the tissues, causing corrosion. This might be due to either the sodium or the hydroxyl ion. As a matter of fact, however, the sodium ion is present in many solutions which are devoid of corrosive effects, for example, in solutions of sodium chloride. The conclusion, therefore, is that the hydroxyl ion is the corrosive in this case. Alco-

hol has no such corrosive action as sodium hydrate, and this corresponds with the fact that alcohol is not an electrolyte, *i. e.*, does not liberate the hydroxyl ion, although it contains hydroxyl. Many other similar examples might be cited, all going to show that in many instances the therapeutic effects of a body are due, not to the molecule administered, but to the ions into which it dissociates in the fluids of the body. In fact in administering an electrolyte, the physician gives not one but two or more substances, which may each effect changes in the organism. As a general rule in therapeutics one ion is so powerful that the other may be neglected; for example, in morphine sulphate the alkaloidal cation is so active that the sulphate ion may be ignored, and the sulphate has therefore the same effect as the hydrochlorate of morphine. When the two ions are more equal in pharmacological activity, however, each has to be taken into consideration; for example, magnesium sulphate dissociates into magnesium and sulphate ions, each of which has a retarding influence on absorption in the bowel, while magnesium chloride similarly forms magnesium and chloride ions, of which the latter is indifferent in the bowel. The sulphate of magnesium has thus a more powerful purgative action than the chloride, and is also more active than sodium sulphate, which forms the purgative sulphate and the indifferent sodium ions.

Another example of the importance of ions to the understanding of therapeutic action and to its successful practice is offered by the bromides. Potassium and sodium bromides have a depressant action on the central nervous system, and as this is absent in the case of the chlorides of these metals, it is obviously due to the bromide ion. Bromated camphor also contains bromine in chemical combination, and attempts have been made to substitute it for the bromides as a depressant. But bromated camphor does not dissociate and no bromide ions are formed, so that whatever properties it may possess, it cannot be compared with the bromides of potassium or sodium.

The action of salts depending on the ions, the intensity naturally varies with the rate of dissociation. This is well exemplified in the local effects of the heavy metals; such salts as the chlorides and nitrates, which dissociate readily, are much more active locally than the sulphates and organic salts which divide into ions less rapidly, provided, of course, that all are equally soluble and have no special characteristics, such as deliquescence. The newer views as to the dissociation of salts and the important rôle of the ions explain why such bodies as the ferrocyanides have the effects neither of iron nor of cyanides, for neither iron nor cyanide ions are formed from them in solution. Similarly the cacodylates differ from arsenous salts because they do not liberate the arsenous ion except after decomposition in the body. Now in the case of potassium arsenite, the arsenite ion is the active constituent, and the cacodylates can possess this only when they are broken down in the tissues into arsenous salts. The slowly dissociating salts are thus often used to avoid the local action of the more irritant metals; for example, many of the recent compounds of iron have the advantage over the older salts of causing less local irritation, while they have practically the same effect on the blood formation. Similarly several new preparations of mercury have been introduced with the view of lessening the local action on the stomach and bowel, or of lessening the irritation induced by the hypodermic injection of mercury. These compounds, when soluble, are more slowly dissociated than corrosive sublimate, and, there being fewer mercury ions present at any one time, the local irritant action is accordingly reduced.

The disinfectant action of the heavy metals also depends largely upon ionization, for the destruction of the germs is due to a chemical reaction between the metal and the protoplasm of the microbes; and the larger the number of free ions the greater the tendency to union. The attempt has been made to obtain germicides devoid of the local irritant action by forming less readily dissociating salts than those in ordinary use. A large number

of preparations have thus been introduced, partly compounds with organic acids, partly with proteid bodies. But as the irritant and the germicidal action of most metallic compounds depend on the same factor, namely, the free ions, it seems likely that the lesser degree of irritation induced by these is obtained only by the sacrifice of much of the disinfectant value.

The double salts are much less readily dissociated than the simple, and not infrequently appear to liberate somewhat complicated ions, as in the case of the ferrocyanides noted above. They are therefore largely devoid of the local action of the parent substances, and this may be taken advantage of in therapeutics occasionally.

When two salts which have one ion in common are dissolved together in water, the dissociation is considerably reduced. For example, if corrosive sublimate be dissolved along with sodium chloride, the former is less dissociated than if it were dissolved alone in the same amount of water. In accordance with this general rule, it is found that the addition of sodium chloride to a mercuric perchloride solution lessens both its irritant and its germicidal power, and in cases in which it is desirable to mitigate the former, and in which the latter is of no importance, as in the treatment of syphilis by the hypodermic method, this mixture may be used instead of the pure mercuric salt.

The complete treatment of the dissociation of salts would involve a large part of pharmacology and therapeutics, in which the importance of the phenomenon is daily becoming more evident. The inorganic materia medica is more dependent on the principle than the organic, as the dissociation is much more complete in the former. It is possible to exaggerate the importance of the new law, however, for many of the facts and principles of therapeutics remain unaltered by its introduction. For example, it is undoubtedly more in accord with modern theory to attribute the effects in epilepsy to the bromide ion than to the bromides, as was formerly done, but this is after all a matter of nomenclature, and it is perhaps necessary at the present time to remember that there was a science and practice of therapeutics before the ion theory was broached. On the other hand, there can be no question that it has thrown much light on many questions, and removed many misconceptions. In the case of the bromides, for example, it is scarcely possible to maintain at the present time that the bromide of ammonium is superior to that of sodium, except possibly in regard to the local action on the alimentary tract, for in each case the active constituent is the bromide ion, and this is equally readily furnished by either salt.

In physiology and biology generally the theory of ions is of great importance, as is at once apparent from the fact that the fluids and tissues of the body can only conduct the electric current through the presence of ions. Every electric stimulus causes a change in their distribution, and every electrical discharge (and electrical changes accompany every movement and every other form of activity) is intimately connected with the presence of free ions, and in fact is possible only in their presence. The whole of electro-physiology, and naturally of electrotherapeutics, has thus to be based on the ionic theory, and the fact that every life process so far investigated has proved to be accompanied by electric changes indicates that the presence of free ions is necessary to life itself. This of course agrees with the fact that inorganic salts are present in every living tissue.

Not only do living tissues require the presence of free ions, but even dead colloid material is altered very remarkably by them. And certain facts have recently been brought out in regard to the dependence of the proteids on certain ions which promise to have a far-reaching influence on biology and hence on medical science. It has long been known that many proteids, notably the globulins, are precipitated from solution when such salts as the sulphates of magnesium or ammonium are added to them. But Hardy has recently shown that the precipitation and solution of colloids, such as the proteids, depend largely on the valency of the ions present in the solution. Thus

bivalent cations precipitate some colloids in comparatively small quantities, and trivalent cations are still more efficacious, while monovalent cations tend to keep them in solution or have a very much smaller precipitating action. The bivalent and still more the trivalent cations thus tend to oppose the monovalent cations in regard to colloid solubility; and as ions are necessary to the life phenomena, the monovalent must be counterbalanced by the bivalent in the tissues, for either of these alone would tend to change the colloids from the normal condition to one of excessive or deficient fluidity.

A good deal of interest has been aroused in regard to the antagonistic action of ions in living tissues, which is found to present some similarity to that described by Hardy in dead colloid matter. The organ examined with most care in this relation is the frog's heart, a very sensitive reagent to changes in its environment. It has long been known that the excised frog's heart will beat for a long time when supplied with oxygenated blood or serum, and also in fluids containing no organic matter, but merely the inorganic salts of serum. On the other hand, solutions of non-electrolytes, such as sugar, fail to maintain the contractions. The presence of ions in the perfusing fluid is therefore necessary to maintain the heart in activity. But all ions are not equally efficient, for a certain amount of sodium chloride is found to maintain the contractions longer than any other single salt. The contractions very soon become weaker in sodium chloride solution, however, and finally the heart is arrested. But this arrest may be prevented if the solution contain in addition to sodium chloride a trace of a calcium salt; on the other hand, a heart which has ceased to beat in sodium chloride solution may be induced to resume its pulsations if calcium be added to the perfusing solution. This phenomenon was first noted by Ringer,* and has been confirmed by all subsequent observers; but views differ as to the interpretation to be given it. Howell has upheld the theory that sodium and calcium are both necessary to the heart, and that when sodium chloride solution is perfused alone, the calcium in the heart muscle diffuses out and is washed away and the heart ceases from its losing one of the necessary constituents, calcium. In support of this view he has shown that when the lime ions are removed by other means, e.g., by precipitating them with oxalates, the heart ceases to beat.

Loeb, on the other hand, holds that the heart can only beat in solutions of electrolytes, and that the least poisonous of these is formed by sodium and chloride ions. Even these are not altogether harmless, however, and after a time the heart ceases from poisoning with the sodium ion. Calcium ions are antagonistic to sodium, and the addition of lime salts therefore reinstates the contractions. To put it shortly, the heart ceases in sodium chloride solution because, according to one view, a necessary constituent, calcium, is all washed out, according to the other, because the sodium is poisonous and has to be antagonized by the lime. Loeb's view appears, at first sight, the less plausible of the two, because it has been held that sodium chloride is a perfectly indifferent substance to animal tissues. It must, however, be remembered that here there is always sufficient calcium present to neutralize any poisonous action of the sodium, and this argument has therefore little weight. On the other hand, he has brought forward some very telling facts in its favor in his investigations of other organs than the heart. Without going into all of these, it may be mentioned that he found striated muscle undergo irregular twitching contractions in sodium chloride solution, but these were arrested by calcium and other bivalent salts, so that the phenomenon is not confined to the heart muscle. Loeb found a small fish, fundulus, which lives in sea water or in distilled water indifferently, but dies in a solution of sodium chloride of the same density as sea

* Ringer's solution, which has been widely used in physiology as that most suitable for conserving the life of tissues, contains sodium, potassium, calcium, chloride, phosphate and carbonate ions and is made up of 100 c.c. of 0.75-per-cent. NaCl, 5 c.c. of 0.25-per-cent. CaCl₂, 2.5 c.c. of 0.5-per-cent. NaHCO₃ and 0.75 c.c. one-per-cent. KCl.

water. This can only be interpreted as indicating that there is something present in sea water which prevents the poisonous action of sodium chloride. On investigating the subject further he found that in a solution of sodium chloride, to which traces of calcium salts were added, the fundulus and its eggs lived as well as in sea water. The conclusion is inevitable that the lime normally present in sea water antagonizes the poisonous action of sodium chloride in this case. The parallel between the behavior of this animal and that of the frog's heart and other organs is so close as to form an important support for Loeb's theory of the interaction of the ions. It may be added that numerous examples of a similar antagonism are already known in more complicated ions than sodium and calcium. Thus the antagonism of atropine and pilocarpine, of curarine and physostigmine in striated muscles, and of the central nervous depressants and strychnine is similar, although these differ in not being essential to the function of the organs on which they act.

It is to be noted that in the case of fundulus, the action of sodium chloride is antagonized by a comparatively minute amount of calcium, and also by corresponding small quantities of other bivalent and trivalent ions, such as those of barium, strontium, lead, zinc, chromium, and alum. Similarly calcium removes or lessens the poisonous effects of potassium salts on the heart, and the potassium ion is also necessary to the normal contraction, so that the antagonism is believed by some observers to be related to the valency of the metallic ion. The fact that electrolytes are necessary to the heart and other organs suggested to Loeb and Mathews the view that the antagonism is due, at any rate in part, to the electric charge carried by the ions, but this is very far from being proved or from being generally accepted. For it has been found that striated muscle, which undergoes abnormal contractions in solutions of several monovalent salts, fails to do so in all; and while the contractions are arrested by some bivalent metals, others have not this effect. The conclusion seems justified that the antagonistic effects are not immediately associated with the valency or the electric charge, but are the results of some unknown special relation between the ions and the protoplasm, these relations differing in different organs and for different metals. In other words, the calcium-sodium antagonism appears to be of the same nature as the atropine-pilocarpine one, and is equally inexplicable in the present stage of knowledge.

While each of the cations alone is poisonous and has to be antagonized by some other cation, ions are necessary to the life processes. Protoplasm can exist then only in the presence of a number of different salts, of which the chief liberate sodium, chloride, calcium, and potassium ions. The poisonous effects of sodium are counteracted by very small quantities of calcium, the ratio obtaining between those in the best media being about 1,000 to 1.

An electric current can be conducted through a watery solution only by means of the ions at liberty in it. The extent of dissociation in the fluid may therefore be estimated by the conductivity of the solution or inversely by the resistance met by the current. As long as there is only one salt in solution the calculation is simple and the results are unequivocal. And however many bodies are in solution, the amount of dissociation may be estimated, although if large amounts of undissociable matter (non-electrolytes) be present the results are too low. But such estimations give no clew to the nature or relative amounts of the salts in solution. Some efforts have been made to apply this method to the examination of the urine and the blood in the hope that light might be thrown on the condition of the kidney by its means. As a matter of fact, however, the urine is much too complex in its composition to permit of results of much value being obtained. The chief electrolytes here are the chlorides, and a small variation in their percentage may induce a large deviation in the resistance, while if the chlorides vary in one direction and the other salts in the opposite, the resistance may remain almost unchanged in spite of great alterations in the composition of the urine. The

chief non-electrolyte is the urea, and its presence in large amount may increase the resistance without any marked change in the amount of salts or their dissociation having occurred. The method cannot therefore be regarded as replacing the chemical analysis of the urine, for its results are of a totally different kind. And it has not been shown by observation that the results obtained by measuring the electrical resistance can be utilized for diagnosis or to indicate the value of therapeutic measures.

Diffusion and Osmotic Pressure.—When distilled water is carefully poured upon a solution of sugar so that the two liquids do not immediately mix, the sugar molecules soon begin to penetrate into the pure water, and after a sufficient lapse of time the contents of the vessel become homogeneous, the percentage of sugar in what was distilled water being the same as in the part corresponding to the original solution. The explanation is that the molecules are in constant movement and, diffusing in all directions, some of them penetrate into the pure water, and this process goes on until the latter contains as many particles as the original. The movement still continues, but now as many molecules diffuse back into the lower layer as into the upper so that equilibrium is maintained. The process is the same as that seen when a crystal of sugar is dissolved, for here also the constituent molecules leave each other and wander throughout the fluid.

When a membrane is stretched between the two fluids, the result varies with its character. If the membrane offers no resistance to the passage of water and sugar, the same phenomenon is observed as if they were not separated by a membrane; the fluid on each side becomes homogeneous, although this generally takes more time, owing to the fact that currents are less liable to aid the process. If the membrane be permeable to neither sugar nor water, of course the fluids remain completely isolated and unchanged. On the other hand, some membranes, known as semipermeable membranes, permit the passage of water and not of sugar. For the sake of clearness, suppose that a solution of sugar be placed in the upper vessel of a diffusion apparatus with a semipermeable membrane, and distilled water in the lower. In this case the molecules of water in the lower vessel can penetrate into the upper, while on the other hand those in the upper cannot escape into the lower. The reason for this is simple; for if water escaped from the sugar solution without an equivalent amount of the sugar, the solution would be more concentrated. Now in order to concentrate the sugar solution, work has to be done; for example, it may be concentrated by heating it. But in the diffusion apparatus there is no source of energy available for concentration, and the result is that the water cannot escape from the upper vessel. On the other hand, the membrane being permeable for water, the molecules in the lower vessel find no difficulty in entering the upper. The result is that the sugar solution becomes more dilute, while the water in the lower vessel diminishes in volume until it may disappear altogether. If sufficient pressure be applied to the sugar solution, the water will cease to enter it from the lower, and the amount of pressure which suffices to arrest the movement of the water is known as the *osmotic pressure* or *osmotic tension* of the sugar solution. The phenomenon is known as osmosis, but it must be recognized that osmosis is merely a diffusion under special circumstances, for the whole is due to the movement of molecules, all of which are free in ordinary diffusion, while some of them (e.g., sugar in the above example) are restricted in their movements in osmosis.

The osmotic pressure is found to vary directly with the number of molecules in the solution, a concentrated solution causing a more rapid flow and a higher pressure than a more dilute one. Thus a one-per-cent. solution of cane sugar exercises a pressure of 535 mm. of mercury, a two-per-cent. of 1,070 mm., and so on. The pressure exercised by even dilute solutions is very considerable, as is seen on transforming these figures into atmospheres, for a two-per-cent. sugar solution is then found to give a pressure of nearly one and a half atmospheres. This is even more remarkable when a smaller molecule than

sugar is chosen. Thus a one-per-cent. solution of potassium nitrate exercises a pressure of over three atmospheres. As the pressure depends upon the concentration of the solution, it decreases and the movement becomes slower as the process goes on, for the water diffusing into the sugar solution dilutes it.

As osmosis is merely a special form of diffusion, it follows that only diffusible and dissolved substances can exercise osmotic pressure. The colloids, such as proteids, are therefore generally believed not to have any influence on the movement of fluids because they are not in true solution, but rather in a state of suspension. Others hold that though in solution, they exercise no appreciable tension because the molecule is so large. As each molecule in solution has the same osmotic effect, it stands to reason that a one-per-cent. solution of sugar must induce an immensely greater pressure than a one-per-cent. solution of albumin, because the number of molecules dissolved in the former is so much greater. The proteids always contain a certain amount of soluble salts, and these are sufficient to cause some osmotic tension; so that it is not yet decided which explanation is correct, but in any case the osmotic pressure of the proteids is so small as to be negligible.

Very often membranes are met which offer a certain amount of resistance to the passage of dissolved diffusible bodies while allowing water to pass freely. If such a membrane separated a sugar solution and water, the latter would at first pass through into the solution rapidly under considerable osmotic pressure. But some sugar also passes downward, and there is thus formed a strong solution of sugar above rapidly being diluted and a weak solution of sugar below rapidly becoming stronger from the continued permeation of sugar into it and the escape of water upward. Finally equilibrium is reached by the solutions on each side of the membrane attaining the same concentration.

The same principles hold when solutions are present on each side of the membrane, the direction of flow being always toward that side on which the larger number of molecules are present, provided the membrane is semipermeable. The osmotic pressure is determined by the difference of the osmotic pressures of the two solutions toward distilled water. If the same body is in solution on the two sides of a permeable membrane, the water tends to pass toward the stronger solution, while the solid passes in the opposite direction until equilibrium is reached. When two different bodies in solution, e.g., sugar and urea, are separated by a membrane which is permeable by each of them, they diffuse freely through it and the two solutions soon become identical, each containing the same percentage of urea and sugar. If the urea can penetrate the membrane while the sugar fails to do so, the osmotic pressure is that of the sugar solution and the urea solution will pass toward the sugar as long as the latter can exert appreciable pressure. In other words, no osmotic pressure is exerted by a fluid toward a membrane which it can pass through.

When neither sugar nor urea can pass through the membrane, the water passes from the solution containing the smaller number of molecules toward that containing the larger number until equilibrium is established by each solution containing the same number of molecules per cent. of water. The weaker solution is often known as the *hypotonic* or *hypoisotonic*, the stronger as the *hypertonic* or *hyperisotonic*, while two solutions possessing the same osmotic pressure are known as *isotonic* solutions.

In biology the problems in diffusion are much more complex than the examples given above, but they all depend on these general rules. In the first place the solutions are much more complicated, containing a number of different substances in solution; in the second, the membranes are neither perfectly permeable nor semipermeable. They permit the passage of some of the constituents of the fluids, but as a general rule few of these pass quite freely, and the amount of resistance varies with each kind of molecule. Further it must be recognized that a dissociated salt exercises not the osmotic tension of a

molecule, but that of its ions. In a dilute solution of sodium chloride, for example, the osmotic pressure is not measured by the number of molecules, for each ion exercises the same osmotic effect as a molecule of sugar, or as an undissociated molecule of salt.

Each cell in the body may be conceived as the inner vessel of a diffusion apparatus, separated from the surrounding fluids by a membrane, for though this membrane has no anatomical existence, the colloid nature of protoplasm has the same final effect as if the cell were surrounded by a membrane. All cells are permeable by water, but each kind of cell appears to differ in the facility with which it permits the permeation of salts and the other bodies dissolved in the body fluids. Some, for example, allow the passage of ammonium readily, while others refuse it entrance. Others take up sodium sulphate as readily as sodium chloride, while others accept the latter and reject the former. Now if the intercellular fluid contains any substance which is not capable of penetrating the cells, it must exert osmotic pressure on the cell; and unless this pressure is counterbalanced by other bodies in the interior of the cell which similarly cannot escape from it, the fluid of the cell will be drawn out and shrinkage will result. Every cell in the body then must be conceived as existing in a condition of equilibrium, the osmotic tension of the salts, etc., in its interior being pitted against that of the surrounding fluid, and the smallest change in either of these leading to an inflow or outflow of water from the cell. Now such changes are continually in progress, for as the proteids and carbohydrates of the cells are broken down into simpler bodies, soluble in water, each molecule so formed acquires osmotic properties, and either diffuses freely into the surrounding fluid, or causes an inflow of water into the cell. In either case the equilibrium is disturbed until the new product is removed by the excretory functions. The importance of diffusion and osmosis in the functions of the body cannot therefore be overestimated; in fact, it may be said that while the more obvious movements of the fluids of the body are determined by the circulatory mechanism, the finer but no less important exchange between the cells and the intercellular fluid is in large part directed by the laws of diffusion. And while a knowledge of the arterial supply of an organ is recognized to be necessary for an understanding of its physiology and pathology, it is probably no less desirable to ascertain the permeability of its cells for the constituents of the surrounding fluids. The osmotic pressure varying with the nature of the membrane or cell, and also with the salt in solution, the only way to determine the results of exposing the cell to a solution of the salt is the experimental, and a considerable amount of work has been done in this direction, so that the permeability of some cells is known for a large number of salts and other bodies. In this method of procedure the cells under examination, e.g., the red blood cells, are exposed to solutions of different strengths, and the concentration which induces neither shrinking nor swelling of the cell is ascertained. This concentration is that balanced by the intracellular fluid, and the solution is said to be isotonic for that cell. The salt in solution must obviously fail to penetrate the cell, or do so only extremely slowly, for if it permeates freely the water in which it is dissolved will also pass into the cell and expand it. In such an isotonic solution the number of molecules percent is exactly equal to that in the interior of the cell, and a solution containing the same number of molecules and ions of any other non-permeating salt will also be isotonic and cause no change in the size of the cell. For example, if a 0.75-per-cent. solution of sodium chloride has been found isotonic for the blood cells, an equivalent solution of sodium sulphate or of ammonium chloride will also preserve the size of the cells unchanged, provided these salts are equally incapable of permeating the cell. If one of these, e.g., that of ammonium chloride causes swelling of the cell and the escape of hæmoglobin, then this salt must permeate more freely than sodium chloride.

In the case of non-dissociating bodies, such as alcohol,

sugar, or urea, equimolecular isotonic solutions can be made by calculating the atomic weights. In the case of the salts this method fails, for the dissociation varies for different salts and for different dilutions, and each ion exercises the osmotic pressure of a molecule. Other methods have therefore been adopted, and of these the estimation of the depression of the freezing point has come into general use in the last few years. This method, it must be emphasized, does not indicate the osmotic pressure for all membranes, nor the permeating qualities of the substance, but only the total number of molecules and ions in the solution. It depends upon the fact that solutions containing the same total number of ions and molecules per cent. freeze at the same temperature, which is lower than that at which distilled water freezes to ice. If two solutions lower the freezing point an equal extent below 0° C., therefore, they contain the same number of ions and molecules, and are isotonic toward a semi-permeable membrane. The estimations are made by means of thermometers reading to 1/100° C., and allowing of approximations to 1/1000° C., and with some care and practice in the method very exact determinations may be made. A very extensive use of this freezing method has been made in experimental work, and some results have also been obtained in clinical medicine, but the details of the method can only be given in works dealing specially with this subject. The depression of the freezing point of any solution below that of pure water is generally expressed by the symbol Δ . If the salt is not capable of penetrating a cell, its osmotic pressure varies with the Δ of the solution, i.e., with the concentration of molecules and ions, and if two solutions of non-permeating salts have the same Δ , their influence on the movement of the fluid of the cell will be equal. On the other hand, if the salt permeates without difficulty, the Δ is of no significance in regard to the effects of the solution on the cells.

The relations of the salts to the tissues has been worked out in most detail in the case of the red blood cells. It is found that in a 0.75-per-cent. solution of sodium chloride, the cells maintain their form and size unchanged, i.e., the salt fails to penetrate the cells and exercises the same osmotic pressure as the diffusible contents of the cells, or is isotonic with the fluid in the interior of the cell. If the cells be exposed to pure water, they swell up and discharge their hæmoglobin, and the same occurs in weak (hypotonic) solutions of sodium chloride. The salt here being in lower concentration than the contents of the corpuscles, a current of water sets inward toward the stronger solution. In solutions of greater concentration than 0.75 per cent. (hypertonic solutions) the cells shrink from the loss of water, which flows outward toward the stronger solution. Similar phenomena are seen when other salts of the fixed alkalies are employed, so that these salts appear to be unable to penetrate the corpuscles except to a very slight extent.

In solutions of ammonium chloride, on the other hand, the cells swell up and lose their hæmoglobin, whether the solution be isotonic with 0.75-per-cent. NaCl, or much stronger. The conclusion is that the ammonium chloride can penetrate the cells and thus exercises no osmotic resistance to the entrance of water, so that the effect of ammonium chloride solution is practically identical with that of pure water. Many other ammonium salts resemble the chloride in penetrating the red blood corpuscles; but others, such as the sulphate and phosphate, fail to enter the cell entirely, or penetrate with great difficulty. The sulphate and phosphate ions, therefore, like the sodium and potassium ions, are non-permeating, and exercise osmotic pressure on the cell wall. Unless both ions of a salt can enter the cell, neither does so. Many non-electrolytes, such as urea and compound ammonias, appear to enter the blood cells freely.

The absorption of salt solutions in the intestine also presents an interesting example of the importance of diffusion in vital processes. A solution of sodium chloride isotonic with the blood is absorbed readily, whence it is inferred that sodium chloride can penetrate the mucous membrane. A hypotonic solution is similarly taken up

easily, and still more readily pure water. A hypertonic solution, on the other hand, disappears from the bowel more slowly, and very often the fluid first increases in the lumen until it has become almost isotonic with the blood, and only then disappears into the tissues. The sodium chloride does not, therefore, permeate the bowel wall without resistance, otherwise a hypertonic solution would be taken up as quickly as distilled water. On the contrary, a hypertonic solution first exercises osmotic pressure on the cells and causes them to lose water. At the same time some of the chloride has disappeared into the cells, and the solution remaining is diluted with the water exuding, until it is so weak that the osmotic resistance is overcome by the absorbing forces and the whole is absorbed into the blood.

When the sulphate of sodium passes into the bowel in solution, this feature is still more marked. An isotonic solution has little tendency to be absorbed, and on the other hand is not increased in volume, the solution in the bowel counterbalancing the osmotic pressure of the cell contents. A hypotonic solution decreases slowly because its osmotic pressure is less than that of the cell contents, and water therefore tends to pass from the weaker fluid in the lumen to the stronger in the blood; but the fluid escapes from the bowel much more slowly than in the case of an hypotonic solution of sodium chloride. If hypertonic solutions be used, the bulk is at first much increased owing to fluid from the blood escaping into the stronger solution. Finally the sulphate solution becomes isotonic with the blood and is very slowly absorbed if the weight of the fluid in the bowel does not set up reflex peristalsis and cause evacuation. This slow absorption from the bowel is still more marked in the case of magnesium sulphate, in which both ions appear to be taken up with reluctance by the mucous membrane. As these salts fail to leave the bowel and retain the water in which they are dissolved, they render the contents more fluid than usual, and the unusual weight and distention cause peristaltic movements and evacuation. The purgative action of the saline cathartics arises from the difficulty with which they enter the epithelial cells. It is to be remarked that here, as in the case of the red blood cells, the sulphates diffuse with greater difficulty than the chlorides; on the other hand, the chlorides of the fixed alkalies are taken up freely by the bowel wall, while they fail to permeate into the corpuscles, and the oxalate of ammonium, which penetrates the blood cells, is rejected by the epithelium.

The presence of the salt solution in the stomach and intestine inducing such movements of fluid into the bowel and back into the blood, naturally causes considerable disturbance in the distribution of the fluids of the body. When a strong sulphate solution is diluted by fluid poured into the intestine, for example, this fluid comes from the blood and indirectly from the fluids of the tissues. A similar exchange without doubt follows the absorption of salt solutions into the blood, but this is difficult to follow experimentally. When salt solutions are injected into the blood-vessels, however, it is found that there is a marked disturbance of the equilibrium of the tissues. If the solution is hypertonic, there is a flow from the lymph spaces toward the blood which continues until the plasma recovers its normal density. The current then is found flowing in the opposite direction from the blood-vessels into the tissues. The lymph measured in the thoracic duct is found to be lessened at first owing to the inflow into the vessels, but later more lymph passes along the duct than usual, owing to the current of fluid passing toward the tissues from the blood.

The injection of salts into the blood-vessels or their absorption from the bowel leads to considerable diuresis. The explanation of this diuresis is still a matter of discussion, but there can be no question that the diffusion and osmotic properties of the salts play an important rôle in this result. The accumulation of fluid in the blood at the expense of the tissues naturally leads to an unusual bulk of the contents of the blood-vessels, and this in turn to an increased pressure in the capillaries. This engorgement of the vessels cannot be relieved by an

outflow into the tissues, for this is prevented by the current of lymph pouring into the vessels. Only one way of escape remains, that through the kidneys, and the inflow of lymph is therefore accompanied and followed by diuresis, which is thus in large part explained by the physical forces, although there is doubtless much still obscure in the process. Different salts vary in their diuretic properties, and this might at first seem to indicate that the diffusion was of secondary importance. As a matter of fact, however, many of these differences can be explained by varying rates of diffusion. For example, the sulphates are as a general rule inferior diuretics when given per os, because they fail to reach the blood for the most part from their cathartic action. On the other hand, sulphate of sodium, injected intravenously, causes much greater diuresis than an equimolecular solution of sodium chloride, even if it causes the same inflow into the vessels and the same degree of hydræmia. This has been explained, however, by the renal tubules failing to absorb the sulphate, while taking up the chloride readily. If this is the case, as appears very probable, the sulphate failing to penetrate the renal tubules and thus return to the blood, must hold a certain amount of water in the tubules which would otherwise return to the blood. The chloride, on the other hand, returns readily through the epithelium lining the tubules, and thus retains less water in the tubules and causes less diuresis. In this view the epithelium of the tubules resembles that of the intestine in repelling sulphates and phosphates and admitting chlorides readily, but differs from it in showing little avidity for urea and sugar.

The urine is generally a much more concentrated fluid than the blood; that is, it contains a larger number of molecules and ions. The kidney must thus do a considerable amount of work in concentrating such a fluid from the more dilute blood plasma, and by estimating the Δ of the blood, which is remarkably constant (about -0.56° C.), and comparing it with that of the urine, the actual work done may be estimated exactly. Dreser calculated the work done by the kidney in forming 200 c.c. of average urine at the large sum of 37 metre kilograms, or over 270 foot-pounds, but this may be greatly exceeded in cases of very concentrated urine. Attempts have been made to use this method of estimating the work of the kidney in clinical medicine, and the subject has been treated of at great length in recent years under the title of cryoscopy. As yet no results of importance bearing on diagnosis or prognosis in renal affections have been arrived at.

When very concentrated solutions of salts or other diffusible bodies are brought in contact with living cells, some fluid escapes from these into the solutions, and this often deranges the activity of the cell. This may be observed in the stomach when strong solutions of such harmless bodies as common salt or sugar are swallowed, the disturbance of the equilibrium manifesting itself in irritation, nausea, and vomiting. In the same way a strong solution applied to wounds or mucous membranes causes irritation and pain from the withdrawal of fluid and precipitation of proteids. The same desiccation of the tissues may arise to a less degree from the presence of excess of salt or sugar in the blood. The organs which suffer chiefly are the brain and spinal cord, as is manifested in tremors and convulsions, and later by paralysis and asphyxia, when strong solutions of salts, sugar, urea, or other diffusible substances are injected intravenously in animals. Arthur R. Cushman.

DWARFISM.—Nanosomia or microsomia is a condition, found in both animals and plants, in which the stature and weight fail to reach the normal minimum for individuals of the same species. The word *nanosomia* is derived from two Greek words, *nanos*, a dwarf, and *σῶμα*, a body, the former being the equivalent of the Latin *nanus* or *pumilio*, the Anglo-Saxon *dwæorg* or *dwerg* and the German *Zwerg*.

From stray references to the subject in the pages of writers of antiquity, we may infer that a belief in the