First Liversidge Lecture.

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Physical Chemistry in the Service of Biology.

WHEN Lavoisier discovered the essential function of oxygen and oxidation in the respiration and life of animals, thus bringing to fruition the earlier views of Mayow, the modern world began to realise that the life and activity of living beings are based on chemical processes. No doubt ideas of this sort may be traced back to much earlier times, though they were incapable of any continuous and exact treatment owing to the rudimentary condition of chemical knowledge. It was the vast development of chemical facts and theories in the nineteenth century which first provided the biological sciences with materials and tools which could be utilised in the study of the phenomena of life.

The first place of honour in this splendid history must be assigned to the science of organic chemistry, which, as the name implies, began as the special study of the complex carbon-containing compounds produced by living things. The extra-vital synthesis of urea by Wöhler, and other similar examples, struck a shrewd blow at earlier vitalistic theories, and inspired in the minds of chemists a great vision of hope, power and usefulness. Perhaps the greatest of those early triumphs of organic chemistry was the elucidation of the nature of the fats by Chevreul. It would, however, be both tedious and invidious to draw up any chronological or other roll of honour in this story of intellectual and practical achievement. One by one, the great classes of complex carbon-containing substances, found in living tissues or secreted by living organisms, have yielded up the secrets of their composition and structure. Purine compounds, carbohydrates, proteins, lipoids, sterols, alkaloids, plant colouring matters—these names represent now daily intercourse in the great household of living Nature. Progress in this field of science is still vigorous and rapid, and will doubtless continue so for a long period of time. To mention only a few examples, the proteins, the complex carbohydrates, and the lipoids offer vast fields of unexplored territory. When to such cases we add the enzymes, vitamins, and hormones, and, no doubt, many things still undreamt of, we obtain some idea of the immense region awaiting exploration and cultivation.

This progress of organic chemistry established the chemical molecule of Avogadro and Cannizzaro as the prime worker in the busy hive of life. It is the molecules which transport the life-giving oxygen and are oxidised or reduced; and it is the molecules that are hydrolysed and broken down, or synthesised and built up, in the mysterious alchemy of the living cell. In the development of organic chemistry we perceive the molecule as the symbolic unit of life.

It would be a great mistake and a grievous error to forget the great services rendered by inorganic chemistry to biological science. Does not water constitute about 75% of the protoplasmic system of a living cell? Even an Archbishop of Canterbury consists very largely of water, though I do not wish to suggest that theology and water are inseparably associated. Life cannot exist without inorganic salts. The protoplasmic system of the living cell contains the chlorides, bicarbonates, and phosphates of sodium, potassium, and calcium. Doubtless other salts are frequently present. Iron, copper, magnesium, manganese, and iodine are known to play various and important roles in the phenomena of life. Organic molecules containing only carbon, hydrogen, oxygen, nitrogen, sulphur, and phosphorus do not reign supreme in the chemical and physical mechanism of the living cell. There are many workers and few drones in the hive of life. Oxygen, water, and numerous inorganic salts play a vital and essential part. They are found not only within the living cells but also in the circulating fluids of the *milieu intérieur* of animals and plants. Life, if it originated on this planet, almost certainly did so on or near the surface of the primeval ocean. Biological science, therefore, owes much to the development of an exact science of inorganic chemistry during the nineteenth century.

During the advance of both organic and inorganic chemistry in that century, attention was largely directed to the discovery of new substances, to questions of composition and atomic structure, and to the study of the nature and relative amounts of the initial and final substances taking part in chemical reactions. But side by side with these studies many others were pursued. Long before the modern science of physical chemistry arose, chemists had taken a deep interest in kindred aspects of their science. In other words, physical chemistry has a history which takes us back at least as far as the eighteenth century. Berthollet and others studied the effects of concentration and temperature, and especially of small solubility and great volatility, in modifying the direction and extent of chemical actions. Much of the work of John Dalton and of Gay Lussac might well be regarded as of a physicochemical nature. Avogadro was a physicist, whilst Volta and Humphry

Davy may be said to have laid the earliest foundations of electrochemistry.

It would be quite inappropriate on the present occasion to trace the development of physical chemistry during the last one hundred and fifty years. It must suffice to remark that gradual and increasing attention was paid to the physical properties of substances and to questions relating to chemical kinetics, to the thermal dissociation of molecules, and to the effects of concentration, temperature, and pressure on chemical equilibria. Biologists did not at first make any extensive use of this growing material, though many exceptions to this general statement will occur to the mind of any historian of that science. For example, physiologists derived considerable aid from the facts and principles relating to the solubility-equilibria of gases and to the laws of diffusion. The remarkable researches of Thomas Graham attracted their attention and were of obvious service and utility. We can indeed draw no hard and fast line, and say that at this date or that biology began for the first time to make use of the results of physicochemical research. It will, however, be doing no great violence to the facts of history if we say that it was the particular science of physical chemistry as created by Raoult, van 't Hoff, Ostwald, Arrhenius, and Nernst which first began to exert a powerful influence on biology. The reasons are not far to seek. Van 't Hoff established the quantitative theory of osmotic pressure and the simple thermodynamical theory of dilute solutions. When physical chemists began to talk of the theory of solutions and of equilibria across semipermeable membranes, they were discussing things of immense interest to every biologist who could think and work quantitatively. Every student of biology knew that the phenomena of life were deeply concerned with dilute solutions and semipermeable membranes. The work of Traube, Pfeffer, and de Vries on osmotic equilibria and the plasmolysis of plant cells acquired at once a deeper meaning and a purely physical explanation. It was clear that another stronghold of the older vitalism was about to fall. The experimental work of Raoult combined with the thermodynamical theory of van 't Hoff enabled the molecular weights of many substances to be determined, which could not be vaporised without decomposition. As the majority of biologically important organic substances are of this character, these new methods came as very welcome aids to the organic and physiological chemists.

It is difficult to exaggerate the importance for biology of the osmotic theory of semipermeable membranes, based on the work of Pfeffer and van 't Hoff. As mentioned previously, three-fourths of the contents of the living cell consist of water. The retention of this water is of vital importance. If too much water leaves the cell, the inner contents become too concentrated and this concentration may easily reach a toxic value. If too much water enters, the cell may burst. What adjusts this beautiful water equilibrium ? The answer of science is simple. It is purely a question of the molecular concentrations of the non-permeable constituents in the fluids within and without the cell, the internal and external plasma. These alone determine the activity of the water molecules within and without, and so adjust the water equilibrium. What at one time would have appeared as a mysterious vital action of the living cell was now explained as a result of the predictable activity of molecules.

The ionisation theory of Arrhenius came as a veritable bomb-shell in the chemical world. Many chemists in this and other countries opposed it very strongly, since it seemed that the kingdom of the molecule was seriously threatened. The ionic theory has, however, triumphed and its development has revolutionised a large part of the theory of solutions. Especially the peculiar condition of acids, alkalis, and salts in aqueous solution, and their interactions and equilibria have been to a large extent elucidated and brought within the scope of quantitative measurement. This transformation of a great range of chemical phenomena has had an enormous effect on biological science. We have only to reflect again on the fact that ionised electrolytes occur as essential constituents of the living cell and the *milieu intérieur* of complex organisms, to realise the fundamental importance of the part played by ionisation and ionic equilibria in the life of animals and plants. The hydrogen-ion activity determines the molecular state and colloidal condition of the amphoteric proteins in aqueous solution, and the optimum activity of enzymes. Little wonder then that it is the hydrogen ion which controls the activity of the respiratory centre in the higher animals and plays an important part in the functioning of muscle and nerve. Little wonder, too, that the delicate dynamic equilibrium of living protoplasm requires a close regulation of the hydrogen-ion concentration. Everywhere this concentration is determined by known or by theoretically calculable ionic equilibria. These equilibria essentially involve the amphoteric proteins, or the protein ampholytes as they are now called. The ionic theory of these amphoteric equilibria we owe to the genius of our fellow countryman, Sir James Walker. It is no exaggeration to say that this development of the ionic theory has been of fundamental importance for the understanding of the phenomena of life.

Young students of the present day can scarcely realise the enthusiasm with which, some thirty to forty years ago, the ionic and osmotic theories were received and applied by active investigators in general physiology and biology. A reference to Hamburger's great two-volume work, entitled " Osmotic Pressure and Ionic Theory in the Medical Sciences," which was published in 1902, will give them a very fair picture of the immediate results of that application, whilst a comparison with the fifth edition of Höber's " Physical Chemistry of Cell and Tissue," published in 1922, *i.e.*, exactly twenty years later, will show the immense development of physicochemical biology during the first two decades of the present century.

It is well known at the present day that the theory of osmotic pressure which we owe to van 't Hoff was a specially simple case, indeed an ideal limiting case, of the general theory given by J. Willard Gibbs, some ten years previously, in his great paper on the " Equilibrium of Heterogeneous Substances." To Willard Gibbs we owe also the thermodynamic theory of chemical equilibrium. Indeed the general theory of those physical and chemical equilibria which play such a great part in the phenomena of life was given by Gibbs in the paper alluded to previously. There is a vast deal more in Gibbs's paper than the thermodynamic principles of osmotic pressure and chemical equilibrium. Some of this has been utilised by later workers, though without doubt much more gold can be obtained from that almost inexhaustible mine.

It may be appropriate here to deal with one particular case. In dealing with the effects produced by semipermeable membranes, Gibbs gives in equation (78)—see page 83 of Volume I (1928 edition) —a condition of equilibrium which must hold when certain constituents can simultaneously diffuse across the membrane in *definite* proportions, these proportions being the same for the solutions on both sides. This condition of diffusion in definite proportions may be provided by the electrical forces, which require that ions must diffuse in equivalent proportions. Later investigations have shown that these ionic distribution or exchange equilibria play an important role in biology, very similar to that played by the osmotic water equilibrium. The outer surface of the protoplasm of the living cell forms a thin, apparently gelated, membrane or skin (Plasmahaut) which acts as a semipermeable membrane. Certain ions, whether simple inorganic ions, such as sodium and potassium, or the large micellar ions of protein ampholytes, may be unable to cross the membrane. This state of affairs produces an unequal distribution of the freely diffusible ions. Such unequal distributions give rise to osmotic pressure effects and to differences of electrical potential. Combined with the water equilibrium, these ionic distribution-equilibria have proved of considerable importance in cellular physiology, and have been very fully worked out by Lawrence Henderson and van Slyke in the case of red blood cells. Those interested in the matter may be referred to van Slyke's book "Factors affecting the Distribution of Electrolytes, Water, and Gases in the Animal Body" (Lippincott & Co.), and to the recently published work on "Blood" by Lawrence Henderson (Yale University Press). Can we speak of crude vitalism defeated by a set of mathematical equations? Perhaps not. At all events, those who read attentively the monographs of Van Slyke and Henderson will experience a singular pleasure in perceiving certain operations of the living cell reduced to mathematical equations derived from the principles of molecular physics. There is undoubtedly a vision of hope, power, and usefulness in such modest beginnings.

The microscopic histology of living organisms demonstrates that membranes and surfaces play an essential role. It might be no great untruth to state that life depends on a relatively gross heterogeneity, in which surfaces and colloid particles constitute the chief morphological elements. The membranes are simply very thin skins with a double surface, one turned towards the outer world, the other enclosing the precious protoplasmic system. The existence of these protoplasmic membranes depends on a labile, varying, and delicate series of equilibria between the inner content and the external fluid or plasma. If the right conditions do not hold within and without, the membrane loses its essential properties or disappears. In either case the complex of phenomena termed "life" vanishes. Whatever may be the real nature of these delicate membranes, it appears certain that the ionic constitutions of the inner and outer plasmas play an important part in determining their existence and proper state. We must, on this ground alone, add the ion as another of the workers in the hive of life. The ion is indeed no poor relation of the molecule. Acting together in friendly co-operation, they help to gather the honey and make the comb.

The importance of surfaces and surface membranes is indeed self-evident when we reflect that the living cell must guard its essential contents from dispersion into the outer world, must select from this outer world the raw materials required for its processes, and discharge thereinto the waste materials whose accumulation would eventually destroy it. We owe to Willard Gibbs very important considerations relating to surfaces of separation between different media. His thermodynamical theory of the accumulation of materials and energy in such thin interfacial films has been extremely useful in physical chemistry and possesses an obvious bearing on the molecular structure of cells and tissues. Modern advances in this subject have, however, travelled in a somewhat different direction. A brief reference to them at this point may be suitable.

There exist at such surfaces of discontinuity powerful uncompensated fields of atomic and molecular force, as a result of which molecules and ions are held or adsorbed, in spite of the general thermal agitation which always tends to disperse them uniformly. These force-fields may be of various sorts. They may be due, as the physicist says, to "van der Waals" forces, or to the forces of electrical dipoles existing in molecules. They may arise from the electrical fields of ions or atom-ions. Some of these force-fields may be of considerable extent and perhaps considerable symmetry, whilst others are undoubtedly highly localised and decrease rapidly with distance. The latter class are of great importance, since they cause the orientation and regular arraying of molecules and ions at surfaces and in surface films. Their action contributes in an essential way to the production of those unimolecular layers which have been so much studied in recent years. Many cases of adsorption at surfaces would be unintelligible if we did not realise the existence of these small intense fields of force which are highly localised in the neighbourhood of "active" atoms or atomic groups.

Let us pause for a moment to consider the importance of these phenomena in biology. A living cell is not merely a little vessel containing salts, proteins, sugars, fats, and enzymes in which chemical reactions occur as in a beaker or flask. There is organisation, and organisation in space means arrangement. In this orientation of molecules and ions at surfaces we may perceive, perhaps, the first faint glimmering of the organised arrangement of the living mechanism. If we assume that this special mechanism is essentially an affair of ions and molecules and their potentialities and powers, then we are almost forced, I think, to search for some at least of its special characteristics, for part of its inner or micromorphology, in molecular arrangement. Perhaps a very rough analogy may help to illustrate this idea. The affinity of hydrogen for iodine at room temperature is less than that of hydrogen for chlorine. Hence in an unorganised assemblage the drive of the hydrogen–iodine affinity cannot dislocate the combination of hydrogen and chlorine. To put the matter more exactly and directly, chlorine displaces iodine from such a combination. I speak here quite roughly and without reference to the ionic theory, as this will suffice for the present purpose. Suppose we construct a number of hydrogen–iodine and hydrogen–chlorine galvanic cells. Each hydrogen–chlorine cell will have a higher electromotive force than each hydrogen–iodine cell. The *E.M.F.* is a measure of the potential of each sort of energy. Now bring in the element of arrangement. Construct a set of cells in series, in which a sufficient number of the hydrogen–iodine cells are working together and against, say, a single hydrogen–chlorine cell. The result will be that hydrogen and iodine will combine together to give hydrogen iodide, whilst simultaneously hydrogen chloride will be decomposed into hydrogen and chlorine. To put the matter in an amusing way, we have here a sort of electrochemical "organism." We feed it with hydrogen, iodine, and hydrogen chloride. As long as we feed it, it operates and does work, excreting hydrogen iodide as waste product, and synthesising the system hydrogen and chlorine. It takes in chemical energy of two different sorts, runs one form down to the lowest possible potential and simultaneously produces a form of chemical energy, smaller in amount but higher in potential than any of the forms taken in. The living cell is very like that, though I will not suggest that this electrochemical "animal" has any direct relation to life. But you can perceive the effects of arrangement, or organisation. Who can say what molecules and ions may not do when suitably arranged or woven in effective patterns that permit the unfolding of their potentialities? There may just possibly exist in the mechanism of life something like an internal electrolysis or atomic movement, occurring in and along oriented and linked chains or other patterns of organised molecules or ions. Such phenomena may occur at or in the protoplasmic membranes. The membrane, the internal granules, and the colloid constituents of the intergranular fluid are all protected by electric layers due to oriented ionic adsorption. The ionic clouds or atmospheres which surround the granules and the colloid protein micelles may act both as buffers and as linkages between these cell constituents.

Adsorption at surfaces must play a great part in the phenomena of life. It is quite possible, nay indeed very probable, that the action of toxins and drugs is due to their adsorption on the protoplasmic membrane. Entrance into the living cell is, of course, not excluded. The suggestion is, however, interesting, and may be important, that the poisoning or toxic action is due to adsorption on the outer membrane surface. Such adsorption, if sufficiently complete, would interfere with the flux of materials across the membrane which is necessary for life. Furthermore, it might well disturb the delicate equilibria on which the existence and semipermeability of the membrane depend. It is known in the poisoning of inorganic catalytic surfaces that very small amounts are necessary, since most, if not all, of the catalytic action is confined to certain particularly active parts of the surface. It is just possible that the apparently undifferentiated surface of the protoplasmic membrane may possess certain differentiated and particularly active parts.

The consideration of the phenomena of adsorption leads to that of colloids. The science of colloid chemistry deals with disperse systems containing small particles varying in size, roughly speaking, between 1 and 200 millimicrons ($\mu\mu$). A millimicron is one millionth of a millimetre, or a ten millionth of a centimetre. These small particles may be little crystals, or extremely large molecules. Very generally they are complex groups or aggregates of molecules and ions known as micelles. Their sedimentation under gravity is prevented by their active Brownian motion, whilst their coherence under the influence of the general forces of cohesion is prevented by the electrical ionic fields and by cushions of water molecules. To the other workers in the hive of life we must undoubtedly add the colloid micelles. They constitute an essential element in the micro-morphology of life. A very great role is due to the electrolytic colloids, or colloid electrolytes, in which at least one polar constituent is an electrically charged ionic micelle, or, at all events, such a very large ion that it exhibits colloid phenomena; for example, that it cannot pass across the semipermeable protoplasmic membrane.

If a colloid system is truly fluid and exhibits no elastic properties, it is called a sol. Under certain conditions the micelles or particles of the sol may cohere or link together to form a framework, and when this happens the sol sets to a gel and generally acquires elastic properties.

Now, needless to say, I have no intention to enter into any details of colloid chemistry or physics. Permit me, however, to refer to a few points. We saw that the retention and loss of water by cells and tissue were explained by the osmotic water equilibrium. That view has been supplemented in recent years by considerations relating to the hydration of gels and their constituent micelles. Various conditions can affect the amount of water held or bound by what are known as lyophilic micelles. The study of such phenomena has opened up new methods of attack on the problems of physiology and pathology. Some idea of the importance attached by modern biologists to colloid phenomena and colloid structures may be gained by a perusal of the monograph on the "Colloid Chemistry of Protoplasm" written by L. V. Heilbrunn and recently published by Borntraeger of Berlin. Even this relatively short monograph contains 43 closely printed pages of bibliography. Modern biologists have examined the colloid condition of the protoplasmic system by microscopic dissection with extremely thin needles, by the movement of inserted iron particles or minute spheres of nickel under the influence of magnetic fields, and by observation of the movements of the granules under the influence of centrifugal force. The last method has been particularly developed by Heilbrunn. What are the results? It appears that the protoplasmic system is enclosed in a thin gelated membrane or plasma skin, derived chiefly from its own contents. Inside this are numerous granules, which are relatively so large that they constitute a fine suspension rather than a colloidal system, *i.e.*, they are visible in the microscope. These granules float in an intergranular liquid which possesses a viscosity only three or four times that of pure water at the same temperature, and exhibits no elastic properties of any sort. It is not therefore a gel. The viscosity of the whole protoplasmic system is only some seven or eight times that of pure water. Besides the granules, there is, of course, in general, the nucleus, and inside the nucleus one or more bodies called nucleoli, and more granules. Spaces known as vacuoles may also occur. Previous to heat death, or to death due to toxic substances, gelation of the protoplasmic system occurs. Heilbrunn suggests that the granules are coated with a layer of adsorbed lipoid material and adsorbed calcium ions. The inorganic salts, proteins, and sugars are supposed to exist chiefly in the intergranular liquid, the nucleo-proteins (as the name would imply) inside the nucleus. The nucleus is itself surrounded by a thin hyaline membrane.

I have ventured to mention these facts on the present occasion, though no doubt they are known to every biologist. I have done so for a very obvious reason. If we accept this picture as a generally valid account of the normal colloid micro-morphology of protoplasm, then we are gazing at the inner citadel of life. At all events, we are gazing at the walls and battlements, even though we cannot see the soldiers. It is of the greatest importance to know whether the sol, rather than the gel, condition is the normal state of protoplasm. In recent years very curious phenomena have been discovered, chiefly by Freundlich and his collaborators. Certain sols under certain conditions pass into a sort of gel state on standing at the same temperature. These gels revert easily to the sol state when gently agitated. Freundlich calls such systems *thixotropic* gels and has given the name *thixotropy* to the phenomenon. It appears that when gelation occurs, the sol micelles arrange themselves in a pattern or framework without actually cohering or coming quite close to each other. The interlocking or binding mechanism may be provided by particularly strong, extensive, and possibly oriented ionic clouds. The question therefore arises whether the sol of the protoplasmic system is not in reality a thixotropic gel. Freundlich has pointed out that under the influence of external magnetic fields small metal spheres are able to make their way freely through a thixotropic gel. The force which propels them is able to break down the delicate structure as the metal sphere moves forward. However that may be, Heilbrunn has brought forward good evidence that the viscosity coefficient, calculated from the movement of the protoplasmic granules through the intergranular fluid under the influence of centrifugal force, shows no variation with the rate of shear. The intergranular liquid, therefore, exhibits no signs of elasticity and must be a true sol. This is a very important result and one which will tend greatly to simplify the study of the protoplasmic system. There can be little doubt that in this study colloid chemistry and physics are destined to play an essential role. The protein framework of life would seem to present a mobile micro-histology lying within that region of dimensions which constitutes the rightful kingdom of colloid science.

Life, however, is not merely an affair of equilibrium and micro-structure, of oriented molecules and ions and delicately balanced micelles. Within and around this framework there exists a continual flux of physical and chemical action. The protoplasmic system operates by utilising the free energy of its environment. It is a free energy converter, utilising the free energy of oxygen plus combustible organic substances, of complex organic substances alone, and of sunlight. It is a physicochemical machine, a dynamical or kinetic system. It is a truism of biology to say that the living organism cannot be considered apart from its environment. But this environment must possess some quality of non-equilibrium. It is the unbalanced environment which is the source of life and action, whilst the living organism is but the energy transformer, though one of a peculiar and still mysterious character. In many respects the active protoplasmic system is like a flame. Its very structure is dynamic—*chemo-dynamic*, in fact. Living things may indeed possess resting phases when life seems almost absent, or at least independent of the environment. But these resting phases may well involve the slow utilisation of internally stored chemical free energy. It is very probable that there can be no life without this direct or indirect and continuous transformation of environmental free energy. If this action stops entirely and irreversibly, the chemo-dynamic structure of life begins to melt away. Here is a field of investigation where physics and chemistry have still a long road to travel before they can render substantial aid to the biologist.

But what do we understand to-day by physics and chemistry? A subtle revolution is taking place in the science of inanimate things. The " organismal " concept is invading physical science and may be studied in the writings of Whitehead and Ritter. The principle of determinism seems to have disappeared from the modern quantum mechanics of micro-systems. Indeterminate specification and statistical probability appear to have replaced the exact specification and deterministic sequence of the older physics. The forgotten philosophy of Karl Pearson has become the mode. " Causes " have lost much of their bright outlines and " effects " are multiple and indeterminate.

These changes are of great import for the future study of biological phenomena. Rigid determinism has always been repugnant to the true believer in biology. Boltzmann, Gibbs, and Smoluchowsky first, and now the modern exponents of quantum statistics have driven that ancient spectre from the physicochemical science of the inanimate. No iron barrier of fixed and inevitable happening now separates thought in physicochemical science from the thought of the biologist. A great mathematician and physicist like Eddington is driven to place consciousness as the background of our symbolic knowledge of the world around and within us. Unimagined and almost unimaginable vistas of thought are disclosed to the vision of the young men of to-day. Growth, adaptation, evolution, volition—these mysteries of life may at no distant future cease to be the enemies of the differential equations of the physicist, for these equations are now but the historic landmarks of a past that is gone. And so we march forward. Let us end by giving praise to the great men of that splendid past. Their work remains, and, like all good work, is valid within its sphere. Where would general physiology be to-day without the thermodynamics created by Mayer, Joule, Carnot, Kelvin, Clausius, and Gibbs ? Where would physical science be without the dynamics of Newton, Lagrange, and Hamilton ? Whatever may be the great biological science of future centuries, it will have been built by many hands. No barriers of thought will separate it from the physics and chemistry of the future. The concept of organism as an " organised whole," which is so essential to biology, has already begun to make way in physical science. Modern mathematics concerns itself much more with order and arrangement than with number and magnitude. There may come a time when a future Liversidge Lecturer will find it fitting to speak of the fundamental contributions of biological thought to the development of physicochemical science, or rather to the development of a homogeneous science embracing all existences and happenings.