at times to possess the opacity and insolubility of a mill-stone; but looking persistently and with care into what appears to be a mill-stone not infrequently proves it to be composed of reasonably transparent material. The members of our institute should take somewhat to themselves as professional men this obscure and difficult problem, and aid in its solution as a matter of their duty to the public.

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## TWENTY-FIVE YEARS OF OSMOTIC PRESSURE IN THE MEDICAL SCIENCES[1]

ON October 14, 1910, a large number of scientific men met in the lecture room of the Botanical Institute at the University of Utrecht, for the purpose of celebrating the twenty-fifth anniversary of Van't Hoff's theory of "osmotic pressure."[2] Professors Ernst Cohen and Hugo de Vries gave the principal addresses. The former, in his most inspiring and finished address, pointed out the invaluable services rendered by this great master to the science of chemistry.[3] Professor de Vries gave a lecture on vacuoles and on this occasion emphasized the importance of physical chemistry in general and particularly that of the theory of osmotic pressure for plant physiology.[4]

[1] Translated from the German by E. I. Werber, Baltimore, Md.

[2] J. H. Van't Hoff, "Lois de l'equibre chimique dans l'etat dilue, gazez on dissons," *Kongliza Swenska Vetenskaps-Akademiens Handlingar*, 21, No. 17, October 14, 1885.

[3] Ernst Cohen, "Een Kwart eew moderne Chemie," *Chemisch Weekblad*, No. 42, 1910 (Dutch); "Ein Vierteljahrhundert moderner Chemie," *Zeitschrift für Elektrochemie*, B. 16, No. 20, 1910.

[4] Hugo de Vries, "Vacuolen, Verhandl. v. h. Provincial Utrechtsch," *Genootschap van Kunsten en Wetenschappen*, 1910, p. 36.

It would, I venture to say, amount to an unexplainable neglect, if the great body of medical investigators failed to give expression to the strong feeling of gratitude to this great scientist.

It gives me pleasure to present a brief account of the researches of de Vries and Van't Hoff and the indebtedness to them of the sciences referred to in the preceding.

In the first half of the last century it was already known that many substances have the power to attract water and also that this power was of great importance for the life of plants. In 1844, Mitscherlich made the first attempt to determine quantitatively this attraction. His figures, however, as well as those of later investigators, were by no means satisfactory.

As late as 1881 Pfeffer, in his text-book of plant physiology, deplores this fact and points out how important for the study of some of the phenomena of life it would be to know, even if only approximately, the water-attracting force acting in each and every substance contained in a plant cell.

It was in the year following (1882) that Pfeffer's hopes were fully realized by the great botanist Hugo de Vries, who actually solved the problem.[5] He employed three biological methods, of which the *plasmolytic* gave the most reliable results. This method consisted in employing a salt solution strong enough to bring about a slight separation of the contents of the plant cell from the cell membrane, in other words, to induce plasmolysis in the cell. Since this separation of protoplasts (plasmolysis) was due to the fact that the power of the surrounding fluid to attract water was somewhat greater than that of the cell contents, de Vries concluded that solutions of other

[5] Hugo de Vries, Proces-Verbal der Konikl. Akad. von wetenschappen te Amsterdam, October 27, 1882; more exhaustively in *Pringsheims Jahrbücher f. wissensch. Botanik*, 14, 1884, p. 427.

salts causing the same degree of shrinkage when acting upon the same cell, must have a water attracting power of the same degree. DeVries called such solutions, *i. e.*, those having an equal water attracting force, *isotonic solutions;* and the simple relations, which appeared to exist between different concentrations of these solutions, he named the *isotonic coefficients.*

De Vries gave a lecture on these researches in the Amsterdam Academy of Sciences, and luckily had in his audience my late teacher and master, Professor Donders, who, as usually, came back to the laboratory in the afternoon. Donders was in the habit of discussing matters with me whenever a scientific problem attracted his particular interest. It was not, I think, that the great man wanted to hear the opinion of his assistant, but rather the fact that these discussions gave him an opportunity to formulate his thoughts and thus helped him to clarify the problem. Sometimes I could not help thinking that my master went a little too far in his thoughts, but this time everything was clear to me. He spoke about the lecture of de Vries to which he had listened a short while before and the question at once arose whether de Vries's findings for the plant cell would hold true for the animal cell.

I began work at once and it was the red blood corpuscles that I chose as my material. The first step was to find a concentration capable of inducing plasmolysis in these cells. But I failed to find it. No plasmolysis could be observed in my experiments. Then I turned to the study of escape of coloring material from the red blood corpuscles. And in the next year my teacher was able to report on my behalf the results of my investigations before the Amsterdam Academy of Sciences.[6] It was actually found that the red blood corpuscles were also subject to the law of isotonic coefficients. Between the concentrations of salt solutions causing the escape of coloring matter from the blood corpuscles the same numerical relation exists as between the concentrations of salt solutions inducing plasmolysis in the same plant cell. *These researches on the blood corpuscles (1883) marked the beginning of modern physico-chemical research in the medical sciences.*

It was repeatedly stated that Van't Hoff's theory of osmotic pressure laid the foundation for these investigations on the blood corpuscles, but this is decidedly a mistake.

The real basis for this work was given in de Vries's researches in plant physiology. These investigations and my own hæmatological researches furnished important data for an experimental proof of Van't Hoff's theory, which was based principally on thermodynamic considerations and on Pfeffer's findings and which was published for the first time two years later (1885). This historical accuracy, it is hoped, may not be regarded as an underestimation of the importance of Van't Hoff's theory for the medical sciences.

It is true that the physico-chemical researches in the medical sciences do not owe their origin to the influence of Van't Hoff's theory and that these researches were continued with success for almost a decade independently of the theory of osmotic pressure.[7] However, it must be strongly

[6] H. J. Hamburger, Proces-Verbal der Koninkl. Akademie van Wetenschappen te Amsterdam, December 29, 1883. German translation in *Festband der Biochemischen Zeitschrift,* H. J. Hamburger gewidmet zur Feier seiner vor 25 Jahren erfolgten Doktorpromotion, S. 1, 1908. Berlin, Julius Springer.

[7] To these belong among others the first determinations of the water attraction power (osmotic pressure) of the blood serum and other animal fluids by means of the study of the escape of the

emphasized that the influence which this theory exerted on the further development of physico-chemical research in medicine has become one of tremendous value. This will become clear from our further considerations.

But even during the decade referred to this theory exerted considerable influence. For some time after its appearance in its completed form (1887) this theory had a stimulating influence, however latent this may have been. Such terms as "water-attracting force" and "isotonic coefficients" no doubt served well the purpose of successful work, but their meaning was rather puzzling and their explanation by the new theory was received like a revelation. Furthermore, the theory of osmotic pressure with its more exact terminology and concepts helped much in shedding new light on what had been accomplished independently of it in the decade above mentioned.

It may well be asked why it was that relatively many years passed before Van't Hoff's theory came to be recognized in the medical literature. An explanation for this, I think, is given in the fact that the theory met with rather unfavorable criticism among the professional chemists[8] and also from the circumstance that the field of work opened up by the theory of isotonic coefficients was so large and the problems suggested by it so numerous that there actually was no time to take into consideration also the theory of osmotic pressure. Besides, for some time—we may well say, in the first ten years—little interest was shown in these new researches and accordingly the number of workers was very scarce. Indeed we were almost alone in our efforts.

However this may have been, that much at least is quite certain, that the theory of osmotic pressure announced in 1885 would not have achieved such great success, had it not been for *the fact that Van't Hoff was able to utilize Arrhenius's theory of electrolytic dissociation as a supplementary one to his own.*

Not infrequently one finds that there are very unclear and inexact notions about this rather intricate matter. It may, therefore, not be uninteresting to give an account of how it developed, using the original publication as a guide.

What was the actual situation?

According to Van't Hoff the dissolved substance, when in a diluted solution, behaves like a gas. He found that in such solutions the particles of the dissolved substance diffuse in their medium, and in this way exert a pressure on the walls of the dish. If a watery solution is made up in a dish, whose walls are semi-permeable, that is, impermeable to the medium of the

coloring matter from the blood corpuscles (1884) and the investigations on the concept of "physiological salt solutions," on the influence of $CO_2$, alkali and acids on blood; here belong also the investigations on lymph, resorption, etc.

[8] An illustration to this we may well see in the following incident:

The board of directors of the Deutsche Chemische Gesellschaft had in 1893 invited Van't Hoff to give a lecture on his physico-chemical researches.

In this lecture on January 8, 1894, Van't Hoff is said to have hesitated between two themes and made the following very significant remark: "On the other hand there was the theory of diluted solutions and osmotic pressure, but I preferred to leave the choice to the directors, *because I should not like to speak on a theme which may at present appear rather undesirable on account of the unfavorable criticism at the hands of professional colleagues, which we all highly esteem.* [Italics mine.] However, the directors chose the theory of solutions." (Cf. J. H. Van't Hoff, "Wie die Theorie der Lösungen entstand," *Ber. der Deutschen Chem. Gesellschaft,* XXVII., I., 1894, p. 6.)

This, then, was nine years after Van't Hoff's famous publication in the Swedish academy.

solution, and if this dish is put into water, the dissolved particles, in their futile efforts to diffuse into the surrounding solution, will cause a pressure. This pressure, which is perfectly analogous to the tension of a gas, Van't Hoff called osmotic pressure. According to Van't Hoff every molecule exerts the same pressure; in other words, solutions of an equal molecular concentration have the same osmotic pressure. This was also proved by experiment, *but only for substances belonging to the same category.* The values of osmotic pressure of substances belonging to different categories were compared, and showed considerable differences. *E. g.*, equimolecular solutions of sugar and salt showed an altogether different osmotic pressure. That of the NaCl solution was $1\frac{1}{2}$ times higher than an equimolecular solution of sugar.

This was the situation in 1885, when Van't Hoff published his theory. No wonder, therefore, that the theory could not be generally accepted.

It fell to Arrhenius's theory of electrolytic dissociation to explain away[9] the difficulty contained in Van't Hoff's theory. According to the Swedish investigator the salts in a watery solution, unlike sugar, dissociate partly into ions. To this Van't Hoff added the idea that each ion exerts the same osmotic pressure as would an undissociated molecule.[10] Accordingly the number of particles causing osmotic pressure is much larger in a salt solution than in an equimolecular sugar solution; in the above mentioned case it was $1\frac{1}{2}$ times as large. This explanation removed the obstacles of Van't Hoff's theory and *the isotonic coefficients of de Vries had now a clear meaning.*

It was now obvious that if the coefficients of NaCl and of sugar were 3 and 2, respectively, this was due to the fact that through the partial dissociation of NaCl into the ions Na and Cl, the number of water-attracting particles became $1\frac{1}{2}$ times larger than that of the sugar solution.

It is then not only to de Vries and Van't Hoff, but also to the great Swedish genius, that we owe a heavy debt of gratitude. This *not only because the theory of electrolytic dissociation forms a necessary supplement to Van't Hoff's original theory, but also because it has itself become of tremendous importance to the medical sciences.*

Without exaggeration, I think, we can apply what Wilhelm Ostwald said in this connection about chemistry, to the medical sciences: "Seldom has a lucky thought thrown so much light on so many and so difficult problems"; and in 1890, *i. e.*, three years after the theory of osmotic pressure has been known in its perfect form, Van't Hoff says of the theory of Arrhenius that "it has almost become a fact."

Quite inestimable has been the influence exerted by the de Vries-Van't Hoff-Arrhenius theory on our sciences. There is hardly a chapter in *physiology* that would not bear signs of this influence.

Nowhere has the application of the combined theory of the three great men been so intensive as in the physiology of the blood. This is easy to understand if we consider the fact that the blood corpuscles unlike most of the other cells can be kept

[9] Svante Arrhenius, "Ueber die Dissociation der in Wasser gelösten Stoffe," *Zeitschr. f. Physik. Chemie*, I., 630, 1887. Cf. also, Arrhenius, Behang till Kongl. Svenska Vet. Akad. Handlingaar, 8, No. 13 and 14, 1884.

[10] Van't Hoff, "Die Rolle des osmotischen Druckes in der Analogie zwischen Lösungen und Gasen," *Zeitschr. f. Physik. Chemie*, I., 481, 1887. He says here: ". . . Thus it may appear that to claim Avogadro's law for solutions as forcibly as I have done it here is rather unwarranted. However, my decision in this matter I owe to Arrhenius, who in a letter calls my attention to the probability that in the case of salt solution and the like we have to deal with a dissociation of ions."

isolated and uninjured for a relatively long time. Another advantage offered by the blood corpuscles is that the influence of diverse agents on their volume and form and likeness on their chemical and physico-chemical composition, can be studied with much exactness. Again it is possible, after causing moderate disturbances in the physiological equilibrium, to observe very accurately the exchange of particles between the blood corpuscles and their natural medium, the blood plasma. Furthermore, an excellent object is given in the white blood corpuscles and particularly in the *phagocytes* for the study of the effect of such disturbances on life.

To these researches belongs among others the study of *permeability* of different kinds of cells. This study was begun in 1889 as one of the results of the theory of isotonic coëfficients. It was found that the blood corpuscles, despite the fact that their volume remains unchanged in an isotonic salt solution, are permeable to chlorine, if kept in the solution for a sufficiently long time. It is hardly necessary to point out how important the problem of permeability is. The permeability enables the cell to admit some substances into its interior and to refuse admittance to others. In this way the troublesome hypothesis of "conscious selection" of cells between certain substances is replaced by a simple fact of physics. To the pharmacologist this means that remedial agents have to be in a form which would make it easy for them to penetrate the interior of the cell body.

It may well be said that so long as physical and physico-chemical methods are employed in the study of the processes going on in living cells, the problem of permeability will play an important rôle in physiology as well as in pathology and in pharmacology.

Of course it must be expected, and many facts have already proved it, that owing to the high division of labor peculiar to the cells of our organism, the permeability to the same substance will be different with the different kinds of cells. So it is, for instance, a well known fact that the epithelium of the intestine is permeable to many substances, to which the epithelium of the urinary bladder is impermeable.

Another important discovery which we owe to physico-chemical researches was made in studying the formation and resorption of lymph. Attention was called here to *a driving force which must be accurately gauged* and which is based on the fact that a movement of water takes place from a place of low osmotic pressure to nearby places where this pressure is somewhat higher. This driving force is rather common, however, and is for instance always found to play a very important rôle whenever a large protein-molecule breaks up into smaller molecules.

Likewise it is the same driving force which, as Starling has shown, owing to the osmotic pressure of the albumen, is so important in connection with the resorption of fluids in serous cavities.

Of course, in the instances dealt with, the differences in osmotic pressure are low; they correspond to only a few thousandths of a degree of the lowering of the freezing point. However, it would be a mistake to think that this difference in the hydrostatic pressure is without influence to the organism. It must not be forgotten that one thousandth of a degree of the lowering of the freezing point would suffice to bring about a driving force of more than 0.1 m. of water pressure and that this pressure does not differ much from the one causing the flow of blood in the capillaries.

These modern researches were of not less importance, for the development of a new branch of science, namely that of *electro-*

*chemistry,* founded by Nernst on Arrhenius's theory of ions. It may well be expected that this new field of investigation will throw much light on problems, whenever electric currents are generated in the organism.

It has been but a few years since electrochemistry has found its application in the physiology of muscles and nerves. The automatic action of the heart as well as the electrical currents accompanying it will very likely find a physico-chemical explanation. These are only a few examples from the field of normal physiology.

Let us now see what was the influence of physical chemistry on other medical sciences.

*Pathological physiology* has gained by important discoveries on the chemical causes of disturbances in the circulation and the genesis of œdema. In *pharmacology* the great achievements in narcotics and disinfection are due in a large measure to physical chemistry.

*Bacteriology* and *histology* have also profited since by the study of permeability and the law of dissociation the nature of the process of staining came to be understood. We now know why it is that certain kinds of cells absorb some substances while others do not; and we also know why the medium of solution of a stain is of such importance in nuclear and bacterial stains.

*Experimental embryology* has gained much by a physico-chemical method of artificial parthenogenesis; and as for *practical medicine,* we may say that there is hardly a text-book or a handbook which does not show the influence of the theory of osmotic pressure. This influence may be found even in *surgery.* Examples of this are the intravenous and hypodermic infusion of the so-called physiological salt solutions and local anæsthesia.

We have attempted in the above to show, by few examples only, how great an influence the theory of isotonic coefficients and the closely related but exact theory of osmotic pressure and that of the electrolytic dissociation exerted on the medical sciences.

Also in an *indirect* way this theory proved extremely important. The brilliant results achieved by it in the last few years have been a stimulus for the application of other branches of physical chemistry to biological problems. It was, for instance, the chemistry of colloids and Van't Hoff's theory of chemical equilibrium and process of reaction that were soon taken up and which, making use of the concept of catalysis introduced by Wilhelm Ostwald, may aid us in understanding the mechanism of *enzyme action.*

To those who desire fuller information on what physical chemistry has given us in a short time, and to become familiar with the names of many of its workers I should recommend consulting some works treating exhaustively on this matter.[11]

It may well be asked how it came that physical chemistry had such brilliant results in our sciences. It is, I think, easy to find the answer to this if we only consider the specific methods of this science. These *unlike* the methods of *analytical chemistry* do not involve the use of strong

[11] Ernst Cohen, "Vorträge für Aerzte über Physikalische Chemie," 2. Aufl., 1907, Leipzig, Wilhelm Engelmann; R. Höber, "Physikalische Chemie der Zelle und Gewebe," 2. Aufl., 1906, Leipzig, Wilhelm Engelmann; von Koranyi und Richter, "Physikalische Chemie und Medizin," 2 Bände, 1907–08, Leipzig, Georg Thieme. Several articles in C. Oppenheimer's "Handbuch der Biochemie des Menschen und der Tierre," 1907 ff., Jena, Gustav Fischer; H. J. Hamburger, "Osmotischer Druck und Ionenlehre in den medizinischen Wissenschaften. Zugleich ein Handbuch physikalisch-chemischer Methoden," 3 Bände, 1902–1904, Wiesbaden, J. F. Bergemann.

bases and acids and life-destroying temperatures. On the contrary, the methods of physical chemistry are of such a nature as to make it possible to investigate the complete structure of many unstable substances of the organism, *in statu quo,* without modifying the changeable equilibrium of the often highly complex systems. This will insure to physical chemistry for an unlimited time to come a very important, and, I dare say, together with structural chemistry, a leading place in the medical sciences.

Far be it from me to underestimate the great achievements of other auxiliary sciences and methods of investigation in medical research. However, they can not lead us as far as does chemistry.

Let us, for example, consider the investigation of electric currents initiated by some physiological processes. No one, certainly, would maintain that the registration of these currents is the final aim of their investigation, even if this were done with faultless technique. Rather would not the question be raised, what chemical processes underlie the curves received by registration? Likewise, it is chemistry which we must expect to help us gain a deeper insight into the nature of and laws governing the processes of gland secretion.

Adapting an utterance of Mach, we may say: "The problems of nature resemble a manifoldly knotted thread, the course of which we can follow now from this and then from another loop which attracts our attention." There is no doubt that in future even more than now physical chemistry will furnish us the loop in our effort to disentangle many an intricate problem.

And the names of Hugo de Vries, Van't Hoff and Arrhenius will forever have a place of honor in the history of medical sciences.

H. J. HAMBURGER

GRONINGEN

## THE COLLEGE MAN IN THE PUBLIC SERVICE

WITH the growth and development of the higher institutions of learning in the United States, the Federal service is attracting and securing an ever-increasing number of college-trained men. The civil-service act of 1883, providing for the gradual application of the competitive-examination method of selecting public officers and employees, opened the door of opportunity in the executive civil service to those whose merit appears from personal demonstration without reference to political affiliation.

With a better qualified personnel, measuring up to higher standards and guided by nobler ideals, there has been a marked increase in efficiency with greater dignity of service as a natural corollary. This marks the triumph of useful knowledge and discipline acquired in schools and colleges, a reminder that "wisdom is justified of her children" in the time and money spent in the cause of education.

It is hardly necessary to observe that the proper performance of the duties of a large number of employments in the public service does not require collegiate training. The lower grades are generally filled by those who have acquired at least the rudiments of education ordinarily obtained in the public schools, and not a few positions are filled by those who have had the advantages of training in special courses for skilled occupations.

Broadly stated, the largest sphere of usefulness in the public service for the college-trained man is found in the military, administrative, and technical offices of the executive branch of the federal government, as well as in legislative and judicial offices.

Positions in the military service, being filled principally by graduates of the government collegiate institutions at West Point and Annapolis, offer careers to comparatively few graduates of other schools. However, there are opportunities for appointment to some places in the military and naval services through competitive examinations held by the respective departments. Among these may be