told that the reality behind the phenomena of sense must be unknown and unknowable, because we can never come at absolute truth. But may not the naturalist be moved to ask whether the conclusion follows from the premises? May it not prove to be only the final transformation of the protean fallacy of the undistributed middle? Instead of showing that we can never know anything as it really is, may not the relativity of knowledge show that nature, as it really is, is relative and dependent—that its being is not in itself? "As no man fording a swift stream," says Huxley, putting into vigorous English a thought that has often found expression; "as no man fording a swift stream can dip his foot twice in the same water, so no man can, with exactness, affirm of anything in the sensible world that it is. As he utters the words, nay, as he thinks them, the predicate ceases to be applicable; the present has become the past; the 'is' should be 'was,' and the more we learn of the nature of things, the more evident is it that what we call rest is only unperceived activity. Thus the most obvious attribute of the cosmos is its impermanence. It assumes the aspect not so much of a permanent entity as of a changeful process, in which naught endures save the flow of energy and the rational order which pervades it."

Every reflective student will, no doubt, feel a responsive chord vibrating in his own thoughts in unison with those of Huxley; but should he not ask himself whether the words, '*flow of energy and the rational order which pervades it,*' mean anything, except that the reality in which the flowing river of nature endures and has its being is rational energy, the energy of a reason, the activity of a mind?

Biological science seems to me to show, with ever-increasing emphasis, that it is in one sustaining mind that we ourselves, and all we know, or can hope to know, have being. Even if this be neither absolute truth nor necessary truth, may it not be that still better truth, a scientific discovery; and the greatest of all scientific discoveries because it has, so far, been verified in every act of knowing?

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THE NATURE OF NERVE STIMULATION AND OF CHANGES IN IRRITABILITY.*

As the conclusions of this paper supplement those of Professor Loeb, and as he is unable at present to publish an account of his work simultaneously with mine, a brief statement of the relationship of our work appears to us both to be desirable.

It is well known that Professor Loeb has for the past several years been applying the conclusions of physical chemistry in the investigation of the phenomena of life, as he was convinced that these conclusions would clear up many physiological phenomena. Of the several discoveries which have rewarded his insight there are two of apparently the most fundamental nature. One of these was made several years ago and published in *Fick's Festschrift* in 1899. It consisted in the demonstration that muscle would only beat rhythmically in solutions of electrolytes. This practically established the fact that contractility was in its essence an electrical phenomenon. About two years ago he expressed to me the opinion that other life phenomena were electrical, and not chemical or thermodynamical. A second fundamental generalization was made last summer at Woods Holl and published in *Pflüger's Archiv*, Volume 88, 1901, to the effect that the toxic and antitoxic action of salts was a function of the number and sign of the elec-

* This paper was prepared for publication early in January, but has been delayed in its appearance.

trical charges their ions bore. During the summer, and later in a lecture before the Medical Society of the University of Chicago, he applied these results to the action of toxines and antitoxines. He was, however, unable to discover any series of facts for the anions similar to those he established for the kations, and he referred the poisonous action of a pure sodium chloride solution to the monovalent kations the salt possessed instead of to the anions. In his work on muscle, also, the stimulating action of sodium chloride was referred to the sodium ions and I provisionally adopted the same explanation in my preliminary paper on the action of salts on nerves published in the *Journal of the Boston Society of Medical Sciences* last spring. Professor Loeb's attention was thus drawn chiefly to the kations. He attributed the undoubtedly greater stimulating action of the bivalent and trivalent anion sodium salts to their calcium-precipitating properties, having been brought to this conclusion by the peculiar action of fluorine.

In 1897 Professor Loeb directed my attention to physical chemistry, and his results on muscle appeared so remarkable that I began, three years ago, a study of the stimulating action of salts on nerves. The relationships were so complex that a long series of observations were necessary, but, during the spring of 1901, I published a preliminary paper in which, owing to incomplete results, I fell into several errors. The stimulating action of the higher anions was provisionally referred to the hydroxyl ions the solutions generally contained, and the peculiar activity of sodium compounds to the diffusion of Na ions into the muscle.

Further experiments showed me that certain of the conclusions were wrong. After reading Hardy's paper on 'Colloidal Solutions' and hearing Professor Loeb's lecture on the possible importance of the valence of ions, and more particularly of the kations, in determining their poisonous character, I had the opportunity of putting together my experiments. After computing the degree of hydrolysis and the number of H and OH ions in the solutions, it appeared that it was not the OH ions which were the cause of the stimulating action of the borates and citrates. The resemblance of my results to those of Hardy on colloidal solutions was apparent, and, apart from certain exceptions left for future investigation, I was led to infer that stimulation was due to the negative ions, and that the positive ions prevented stimulation; and also that as the stimulating action of the anions generally increased with an increase in valency, the stimulation was due to the electrical charges the ions bore. Following out this idea, which, as will be seen, was the extension of Loeb's idea of the importance of valence, the electrical relationships of nerves, the nature of stimulation and of changes in irritability and the nature of the nerve impulse appeared in a new light. The main results and conclusions were presented before the Medical Society of this University on December 2.

Meanwhile, unknown to me, Professor Loeb had begun to doubt that the calcium precipitation by the higher anions was the real cause of their action. Upon hearing my results and conclusions he perceived that they agreed with his facts as well.* It is with gratitude that I acknowledge my indebtedness to Professor Loeb, who showed me in which direction to look and who as a pioneer has opened one of the most fruitful fields of science. My own conclusions supplement and, it seems to me, make more precise those general ideas which were guiding him.

* Since this paper was sent to the editor, Professor Loeb has published in the February number of the *American Journal of Physiology* a portion of his results on muscle.

My observations were made on the sciatic nerve of the frog and stimulation of the nerve was shown by the contractions of the gastrocnemius muscle. I have tried about nine hundred experiments on frogs at different seasons of the year, so that the observations are numerous enough to offset most individual variations. The nerves were immersed for the greater part of their length in the solutions to be tested.

1. Nerves are stimulated by the withdrawal of water. The non-electrolytes sugar, urea and glycerine will stimulate if the osmotic pressure of their solutions is equal to, or greater than, twelve atmospheres. This is more than twice the osmotic pressure of the nerve. Nearly all electrolytes tested, quite irrespective of their nature, will also stimulate if their solutions are as concentrated as this. The nerve always increases in irritability (katelectrotonus) before impulses large enough to cause the muscle to contract are generated. After complete loss of irritability in the non-electrolytes the nerves will be completely restored by placing them in M/8 sodium chloride solution. These facts demonstrate anew the truth of the generally accepted opinion of physiologists that the change in the nerve which generates the nerve impulse can be set up by the withdrawal of water.

2. All salts of H, Li, K and NH_4 which were tested of which the anions are monovalent, such as KCl, KBr, KI, LiCl, NH_4Cl, and others; all salts of bivalent kations united to monovalent or bivalent anions, such as $MgCl_2$, $MgSO_4$, $Mg(NO_3)_2$, $ZnCl_2$, $ZnSO_4$, $BaCl_2$, $Ba(NO_3)_2$, $CuSO_4$, $SrCl_2$; all salts of trivalent kations united to monovalent anions, such as Fe_2Cl_6 and Al_2Cl_6 will generally stimulate if their solutions have an osmotic pressure of twelve atmospheres or over. In solutions weaker than this they all annihilate nerve irritability without stimulation, H, K and Fe_3 salts most rapidly. Irritability may generally be restored, if the nerves are not left too long in the solutions, by immersion in M/8 NaCl solutions. All these salts, therefore, stimulate by withdrawing water. The salts themselves will in each case destroy irritability.

3. All acids tested with the exceptions (possibly) of phosphoric and oxalic will not stimulate, except in solutions of high osmotic pressure (twelve atmospheres). Hydrogen ions do not appear hence to stimulate the nerve. On the contrary in weaker solutions tested, nerve irritability was lost without stimulation. This confirms Grützner and others. My experiments, however, are not complete on this point.

4. Alkalies such as NaOH, LiOH, KOH, $Ba(OH)_2$ will stimulate in approximately N/20 solutions. The hydroxyl ion, in other words, at certain concentrations stimulates the nerve.

5. If we compare the stimulating action of NaCl, NaBr, and NaI we find that these salts stimulate even in solutions of the same osmotic pressure as the nerve. The stimulating action of the salts increases as we pass from the chloride to the iodide. Hence stimulation is in some way a function of the anion, because the rate of diffusion of these salts is approximately the same and the number of Na ions is constant. It is not a function of the atomic weight, since the fluoride stimulates more than the chloride or iodide. These observations confirming Grützner led to the conclusion that the stimulating action of salts is due to their anions. On comparing the action of Na_2SO_4, $Na_2C_2O_4$, Na_2HAsO_4 and other bivalent anion salts we find that these are more powerful than the monovalent anions; and the trivalent anion salts such as sodium ferricyanide, sodium citrate and Na_3PO_4 are still more powerful than the bivalent anion salts. Thus NaCl and NaBr

will stimulate slowly in solutions of one gram molecule to 8,000 c.c.; Na_2SO_4 in one gram molecule to 25,000 c.c.; and Na_3 citrate in solutions of one gram molecule to 50,000 c.c. The power of stimulation as indicated by the prolonged tetanic and simple contractions of the muscle extending over hours is also greater than that of the monovalent salts. These observations clearly support the inference that stimulation is a function of the anions and also establish the fact that it is a function of the charges the ions bear. They thus support Loeb's general idea that valence or the electrical charges of ions determine their physiological action, but demonstrate that it is the negative ions which stimulate. As will presently be shown, however, valence, as such, possibly has no direct influence, but only indirectly determines the action of these ions.

6. The conclusions just drawn led me to infer that the positive ions must prevent stimulation and render the nerve non-irritable. This is shown to be the case by a comparison of HCl, LiCl, KCl, NH_4Cl and NaCl. The last salt stimulates; in the others the chlorine ion will not stimulate and the nerves lose their irritability. This can only be explained, I believe, by assuming that the stimulating action of the chlorine ion is overbalanced by the non-stimulating action of the positive ion, and of these positive ions it appears that H overbalances most, K less, Li still less and NH_4 least. If this idea is true it should be possible, by combining these positive ions with di- and trivalent more potent anions, to obtain a stimulating compound. This is indeed the case. KCl never stimulates except by the withdrawal of water; K_2SO_4 will occasionally stimulate the most irritable nerves in solutions of about the osmotic pressure of the nerve; K_3 citrate and K_3 ferricyanide will stimulate in solutions of a gram molecule to 22,000 c.c., of which the osmotic pressure is less than that of the nerve. The same is true for other salts. Li_3 citrate stimulates in a gram molecule to 30,000 c.c. and $(NH_4)_3$ citrate in a gram molecule to 40,000 c.c. We thus come to the conclusion that stimulation is due to the negative charge of the anions and that the kations prevent stimulation. It follows from this that the chemical properties of an acid or a salt are determined by the balance between the anion and the kation. In NaCl the ions are nearly equivalent, but the chlorine slightly overbalances. This idea of the mutual antagonism of the anion and kation may possibly throw light on chemical processes and properties generally.

7. $KMnO_4$, $NaMnO_4$, and $NaClO_3$ will stimulate in solutions of a gram molecule to 12,000 c.c. This stimulation is possibly due to the liberation of some bivalent oxygen anions.

8. These results are similar to those of Hardy and others on colloidal solutions. Colloidal solutions, the particles of which are positively charged are precipitated by OH ions and anions and the precipitating action of these anions is in proportion to a power of their valence. They seem to be held in solution by hydrogen and possibly other positive ions. As it is well known that protoplasm contains colloids in solution, a fact Hardy has particularly emphasized, it occurred to me that stimulation might be due either to a gelation of the colloids or to their passage into solution. Loeb has frequently mentioned his belief that a variation in the state of the colloids in protoplasm is of importance in protoplasmic activity and particularly irritability. He and others have repeatedly described processes of liquefaction of protoplasm, and several years ago he attempted to refer changes in irritability to an alteration in the viscosity of protoplasm. I infer that stimulation consists in a

passage of the particles from the solution to or toward the gel, and that if we can prevent gelation stimulation is prevented and irritability is lost. This is indicated by the following facts among others:

The nerve contains colloids. Colloidal solutions, the particles of which carry positive charges, are precipitated by negative ions. Nerve irritability is increased by cooling and diminished by warming. The stability of the hydrosol is probably diminished by cold and increased, like common gelatine, by moderate warmth. Also when coagulation by heat occurs the nerve is stimulated. Coagulation is but the formation of an irreversible gel. Darwin's observations on *Drosera* and other plants by optical evidence demonstrates also this gelation. Darwin observed in his work on 'Insectivorous Plants' that the passage of the impulse over plant cells, which corresponds to the nerve impulse in animals, was accompanied by a visible precipitation or gelation of the protoplasm, the nature of which he did not understand, but which he called aggregation. He states that the molecular change supposed to occur in nerves may thus actually be seen in plant cells. There can be no doubt that he was right in comparing this change to the nerve impulse. He found that it was produced most readily by the citrates and phosphates, and was checked by Ba, K and other such salts. Thus his facts correspond closely with those I have found for the nerve. Aggregation was prevented by ether, by CO_2 or lack of oxygen. It could be produced by the extraction of water. His description of the process leaves little doubt that he is describing the formation of a reversible gel. The aggregated particles afterwards dissolved. The action of anæsthetics and the electrical phenomena of the nerve also support the idea that stimulation is a process of gelation. This will be discussed later.

These facts indicate the truth of the following general statements:

I. Protoplasm consists essentially of a colloidal solution, the particles of which are positively charged. It is a reversible hydrosol.

II. Stimulation consists in the passing of the solution to or toward the gel. Irritability is reduced or abolished if we make the sol state more stable, or if gelation is complete. In other words, irritability varies inversely with the stability of the hydrosol.

9. Electrical stimulation. If stimulation is due, as I believe, to the negative charges the ions bear and is prevented by the positive, the identity of electrical and chemical stimulation is thus demonstrated. It makes no difference whether we put the negative charges into the nerve on ions or whether by touching the nerve with electrodes we bring about, so to speak, a surplus of positive charges at one pole and negative at the other. The end result is the same. It is thus plain why the stimulus begins at the negative electrode, or kathode. In this region by the action of the kathode, the negativity of the nerve is increased and gelation occurs. In what manner this negativity is increased will be discussed in the full paper, but it may be due indirectly to the hydroxyl ions. Electrotonus is also explained. By the passage of the current the negative charges are in excess or preponderate in their action near the kathode and positive charges preponderate near the anode. The stability of the hydrosol is diminished near the former and increased near the latter. Irritability is altered as just explained. These conclusions are supported by Hardy's observations on the movement of colloidal particles in the electric current and their precipitation at the kathode if positively charged. If the nerve is already near gelation (very irritable by cold or drying) we may have

gelation occurring sufficiently abruptly to cause tetanus during the passage of the current. A true condition of katelectrotonus may also be produced by taking water from the nerve.

10. The current of injury may also be explained on this hypothesis. At the cut end aggregation or gelation is taking place as a result of the disturbance of the mechanical conditions of the nerve. Here positively charged colloids are going out of solution and negative charges are temporarily set free. The cut end becomes negative to the uninjured portion. This conclusion is supported by the fact that warming the nerve locally causes the warmed portion to become electro-positive to the unwarmed, and cooling it causes the cooled portion to be electro-negative to the rest of the nerve. It is similar to what occurs when zinc goes into solution. The undissolved zinc becomes negative to the solution. It is also well known that if by heat we produce an irreversible gel (artificial heat section) of the nerve, the coagulated portion is negative to the rest.*

11. Mechanical stimulation may possibly be understood as follows: By the mechanical coalescence of the neighboring colloidal particles their surfaces become less than the sum of the surfaces of the separated particles. A portion of the negative charges formerly induced in the water surrounding each particle is accordingly set free. These immediately act like negatively charged ions and precipitate the next layer of colloids. The process may possibly be similar to that which occurs on jarring an unstable hydrosol or a supersaturated solution. The observations of Darwin and others show that jarring will bring about aggregation in protoplasm.

12. The nerve impulse may consist in the following process. By the precipitation of each layer of colloids negative charges are regenerated; these precipitate the next layer of colloids and are again regenerated, and so on. That something of this sort occurs is indicated by the following facts:

(*a*) Darwin's observation that the passing of the impulse in plant cells is accompanied by a progressive precipitation.

(*b*) The facts that negative charges are set free in the nerve by the action of each successive segment. These charges constitute the negative variation.

(*c*) The fact that negative charges precipitate positively charged colloids.

(*d*) The fact that negative charges stimulate the nerve.

(*e*) The fact shown by the action of ether and other poisons that the negative variation is not a simple movement of inorganic ions, but is dependent for its propagation upon the state of irritability (state of the colloids) of the nerve. This fact has already led many physiologists to infer that the negative variation stimulates each successive segment of the nerve and is regenerated by the change it itself has brought about.

13. The action of anæsthetics. This consists, on the hypothesis so far sketched, in increasing the stability of the hydrosol or solution, and so preventing precipitation. There can be no doubt that the anæsthetics have this action as is shown by the following facts: Darwin observed that they prevent the process of aggregation or precipitation in plant cells, and it has been shown by Loeb, Budgett, Zoethout and others that they liquefy or dissolve the cells of infusoria and other animals and egg cells. The effect of a mixture of ether and water on starfish eggs is remarkable. The egg dissolves in it very rapidly. Furthermore, Overton and Meyer have shown that the anæsthetizing action of substances is pro-

* The relation of this explanation to Waller's idea that the cut end is positive will be discussed in the full paper.

portional to their fat-dissolving powers. The colloids in protoplasm are in all likelihood fat or lecithin proteid combinations like the sheath of the red blood corpuscles, and like the latter they are, no doubt, more soluble in ether and water than in water alone. So far as I can see, this explanation of the action of anæsthetics is in harmony with the facts. It supports the general conclusions drawn as to the meaning of changes in irritability and it explains the often-noted similarity of action between hydrogen ions, certain poisons, potassium ions and the anæsthetics. All these substances increase the stability of the hydrosol and liquefy protoplasm.

14. Stimulation by light and ether vibrations. In paragraph 5 it was stated that, in my opinion, stimulation by the negative ion was not due primarily to the valence of the ion. It is not the charge itself, but its motion, which determines stimulation. This is shown, I believe, by the variation between the action of fluorine, chlorine, bromine and iodine, and between potassium, sodium and hydrogen. The hydroxyl ion, although monovalent, stimulates like a bivalent anion. Since the fact is apparently established that it is the electrical charge which stimulates, and not the atom with which it is associated, and also since the charge associated with chlorine does not differ in nature from that associated with fluorine, the difference in action between these ions can only be due to something the charge does; in other words, to the motion of the charge or of the atom with which it is associated. When a charge is moved it produces a disturbance in the ether. It is well known to all that the vibrations of the ether will produce those changes in protoplasm which the ions produce, and further the character of the change in protoplasm produced by light varies with the wave-length or the number of impacts per second. Violet light or the ultra-violet rays stimulate protoplasm, while the red rays as a rule do so very feebly or inhibit movement. By the electromagnetic theory of light the ether disturbances which we call light must be due to the movement of electrons or charges in the sun, either constituting a part of the sun's atoms or associated with these atoms. In other words, it is not the presence of the charges in the sun which stimulates protoplasm, but the movements of the charges.

These facts are ground enough for the hypothesis that it is not the charges or the number of charges, but the movements of the charge which produce the change in protoplasm called stimulation, and, I may add, which must determine chemical action as well. This idea will agree, I believe, with the suggestions of J. J. Thomson, Larmor, Nernst and others in regard to the association between atoms and electrons. This motion of the electron may be either translatory on the atom, which will agree with the kinetic theory of solutions, or it may be a rotatory motion. For various reasons I am inclined to assume that the charge is either revolving with the atom or about it, but a detailed consideration of this point will be given in the full paper. Knowing, however, that charges in motion affect the ether; that the impulses thus given produce chemical changes; that substances in solution or as solids actually give out what we call ether vibrations; having established the fact that monovalent ions differ among themselves in stimulating action, although the charges are the same on each, and also that ions stimulate by the charges and not by the atoms, I see no escape from the conclusion that it is not the charge, but its motion and its sign, which ultimately determines its action. In other words, chemical stimulation and light stimulation are identical.

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