THE NATURE OF CHEMICAL AND ELECTRICAL STIMULATION.

BY WILLIAM SUTHERLAND.

UNDER this heading A. P. Mathews has given a suggestive interpretation of his numerous experiments on the nerve-stimulating action of electrolytic solutions. He shows that a fair measure of the stimulating power of an ion is obtained on dividing the square of its ionic velocity by the product of its solution tension and the square root of its atomic mass, namely, \( \frac{V^2}{E W^{\frac{1}{2}}} \). He admits the difficulty of giving a theoretical justification of this measure, pointing out that when \( E = 0 \), it becomes infinite. When \( E \) becomes negative, he transfers it from the denominator to the numerator. In these circumstances it seems hopeless to seek for a theoretical deduction of \( \frac{V^2}{E W^{\frac{1}{2}}} \) as the proper measure of the stimulating power of an ion. Profiting by the pioneering of Mathews, I have been led to the following quite simple theory of his results according to the principles of physical chemistry.

It is helpful to distinguish two chief ways in which a nerve may be stimulated electrically,—first, by electric force without the passage of external electricity into the nerve, and, second, by the actual passage of electricity into the nerve. It is proposed to show in the following that in the experiments of Mathews negative ions stimulate nerve by giving to it their electric charges, whereas positive ions do not give their electrons to a nerve, but depress it through the action of their electric force. According to this distinction all negative ions of the same valency, having therefore the same electric charge, ought to have the same stimulating action, namely, that of giving that charge to the nerve; but, on the contrary, positive ions of the same valency, though having the same electric charge, ought not to produce

\[ ^1 \text{Mathews: This journal, 1904, xi, p. 455.} \]
the same depressing action, because, being of different sizes and of different dielectric capacity (specific inductive capacity) they have different electric forces at their surfaces. If \( a \) is the radius of an ion and \( K \) its dielectric capacity, \( v \) its valency, and \( e \) the electron charge, the electric force at its surface is \( \frac{v e}{K a^2} \). The charge \( v e \) will produce an inductive charge in the nerve proportional to \( v e \); so the actual force on the nerve will be proportional to \( \frac{v^2 e^2}{K a^2} \). The most striking result obtained by Mathews is contained in his Table IV, which shows that for ten out of sixteen salts of sodium with monovalent acids the minimum strength of a stimulating solution is one-twelfth gram-molecular, or \( \frac{m}{12} \). For sodium iodide it is \( \frac{m}{15} \), and for sodium hydrate, the most important exception, it is \( \frac{m}{90} \). With due allowance for the exceptions, the generalization is clear, that negatively charged monovalent ions have the same stimulating power. When the formic, acetic, and butyric anions stimulate to the same extent as the chlorine and bromine ions, which are so different from them, we have clearly to do with a fundamental relation. In the case of the sodium salts of bivalent acids, with the exception of acid salts and the carbonate borate and bichromate, the minimum stimulating concentration is \( \frac{m}{32} \). With sodium citrate, the case best representing trivalent acids, the concentration is \( \frac{m}{50} \). Now, in considering these numbers 12, 32, and 50, we must remember that the stimulation of a cut nerve is essentially a surface phenomenon at the severed end. Hence in the present connection we ought to consider the number of molecules per unit surface and not the number per unit volume. So we ought to compare \( 12 \frac{1}{3}, 32 \frac{1}{3}, \) and \( 50 \frac{1}{3} \), namely, 5.24, 10.08, and 13.57 as measures of the number of molecules of sodium compounds with mono-, di-, and tri-valent acids which just stimulate. But as the acid radicles of these types carry 1, 2, and 3 electrons, we get for the measure of the stimulating power per electron the values 5.24/1, 10.08/2, and 13.57/3, namely, 5.24, 5.04, and 4.52. These numbers are not identical, as they ought to be to confirm sharply the important principle that stimulation by solutions is a surface action; but they agree well enough to help confirm a later calculation involving the principle of surface action as fundamental. Their mean value is 4.9.

With the salts of potassium and ammonium the experimental results are not so clear cut, though on the average they confirm the prin-
ciple of surface action satisfactorily. The minimum stimulating concentration for salts with monovalent acids is about 4.5, for divalent acids 14, and for trivalent 20 in the potassium citrate and 30 in the ammonium citrate. If we take 4.5, 14, and 25 as mean values, and raise them to the $\frac{2}{3}$ power in order to compare effects per unit surface, we get 2.73, 5.81, and 8.55, which upon division by 1, 2, and 3 respectively give 2.73, 2.90, and 2.85. Here the agreement is as good as possible under the conditions. For the lithium salts the data are few, and give 3, 10, and 30 for the minimum stimulating concentrations for the three classes of salts. Taking the $\frac{2}{3}$ power of these and dividing by 1, 2, and 3, we get 2.08, 2.32, and 3.22. Here the last number is markedly discrepant.

The other result of importance concerning negative ions found by Mathews is the exceptional behavior of OH. The minimum stimulating concentration found for the hydrates is $\frac{mL}{20}$ for Na, $\frac{mL}{20}$ for K, and $\frac{mL}{18}$ for Li, while it is $\frac{mL}{40}$ for Sr. For all hydrates it is about $\frac{1}{20}$ gram-equivalent per litre. Here the positive ion seems to be of no account. Probably there is a different chemical action between nerve and alkali from that between nerve and neutral salt, the OH concentration at the nerve being so much increased that the positive ion of the hydrate never gets near enough to the nerve to make its field of electric force effective. Amongst negative ions OH is remarkable for the large ionic velocity usually assigned to it. In a paper contributed to the Philosophical Magazine I have sought to show that the OH ion does not really have this exceptional velocity, but that it dissociates a certain amount of water into H and OH ions whose velocities are credited to the original OH ion. This exceptional power of the OH ion is doubtless partly the cause of its exceptional behavior in stimulating nerves. By using the result 20 to measure the stimulating power of an equivalent of hydroxide, we might make an attempt to separate the stimulating and depressing parts of the action of a dissolved salt.

If $20^2$ measures the stimulating power of the OH ion, its value, 7.4, may be taken to give the power of all negative ions. Hence, since 4.9 measures the power (of electric origin) of such types as NaCl and $\frac{1}{2}$ Na$_2$SO$_4$, we get the depressing power of the Na ion as 2.5. For equivalents of K, Li, and NH$_4$ salts the stimulating power is about 2.8; hence the depressing powers of K, Li, and NH ions are about 4.6.

Special interest attaches to the H ion of acids. Its action appears
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most clearly in the experiments on acid salts. While the minimum stimulating molecular concentration of Na₂SO₄ is $\frac{3}{2} \times 9$, that of NaHSO₄ is only $\frac{1}{3}$. Hence the depressing power of the H ion per unit surface exceeds that of the Na ion by $\frac{32\frac{1}{3} - 6\frac{2}{3}}{2}$, or 6.8. With K₂SO₄ and KHSO₄ the difference in the minimum stimulating molecular concentrations is only that between 5 and 4, K₂SO₄ being markedly exceptional. NaH₂PO₄ stimulates in concentrations $\frac{m}{l}$ per litre, so $6\frac{2}{3}$ measures its stimulating power per unit surface. For Na₃PO₄ the normal power would be $50\frac{2}{3}$. In this case the depressing power of the II ion exceeds that of the Na ion by $\frac{(50\frac{2}{3} - 6\frac{2}{3})}{2}$, or 5.1.

On the average the depressing power of the H ion exceeds that of the Na ion by $\frac{(10.2 + 6.8)}{3}$, or 5.7. But the depressing power of Na was tentatively estimated above at 2.5, so that the depressing power of H is 8.2. Now the stimulating power of an equivalent of an ion was taken at 7.4. It seems to me to be the safer conclusion to state that the depressing power of H is about equal to the stimulating power of a monovalent negative ion. From this it would appear that the H ion differs from other positive ions in being able to give up its positive charge to nerve like a negative ion. As regards ionic velocity, the H ion is still more exceptional than OH, according to the values hitherto accepted. Just as in the case of OH I have sought to show that the true ionic velocity of H is not exceptional, but that the H ion splits about twice as much H₂O into H and OH as the OH ion does, and is credited with the velocities belonging to these products of its action on water. Now in certain cases, as for instance that of globulin, the action of acids and alkalies on proteids is far more like a definite chemical one than that of neutral salts. On this account the positive charge of the H ion may be given up to nerve in a way not possible to the positive ions of neutral salts. If the depressing action of the H ion is equal to the stimulating action of monovalent negative ions, then acids ought to have neither a stimulating nor a depressing effect on nerve. In his experiments Mathews found the acids to possess a small stimulating power, which he attributes to other causes than those now under investigation. In another way he showed hydrochloric acid to have a depressing power much greater than the stimulating power of sodium chloride or rubidium chloride. It seems to me, however, that it is necessary to distinguish two sorts of depressant action, namely,
that associated with permanent chemical change in the nerve and that not so associated. For example, the salts of heavy metals such as copper and mercury most probably form irreversible precipitates in contact with nerve. This chemical effect complicates the physiological investigation of the purely ionic electrical effect. The clearest fact about the H ion is that it is a powerful depressant. The evidence, on the whole, goes to show that its depressing power is about equal to the stimulating power of a negative ion equivalent.

The next business is to study comparative values of the electric force acting on the nerve at the surface of the different positive ions, \( \frac{v^2 e^2}{K \alpha^2} \). Values of \( K \), the dielectric capacity of the stuff of the ion, are taken from "The Dielectric Capacity of Atoms,"\(^1\) as also values of \( B \), the limiting volume of a gram atom, \( B^\frac{3}{2} \) being proportional to \( \alpha^2 \).

As we desire to compare the action of equivalents, we must divide \( \frac{v^2 e^2}{K \alpha^2} \) by \( v \) to get the effect to be ascribed to each electron charge \( e \) in the ion. So in the subjoined table are given values of \( \frac{1000v}{K B^\frac{3}{2}} \) to represent those of \( \frac{v^2 e^2}{K \alpha^2} \), which we wish to study. For Mg, Ca, Sr, and Ba \( v = 2 \), and for the rest \( v = 1 \).

\[ \begin{array}{cccccccccc}
 & H & Li & Na & K & Rb & Cs & NH_4 & Mg & Ca & Sr & Ba \\
 K & 2.07 & 6.27 & 3.24 & 1.62 & 1.28 & 1.08 & 1.67 & 6.58 & 5.16 & 4.72 & 3.83 \\
 B & 8.00 & 2.00 & 7.40 & 3.40 & 34.40 & 50.00 & 18.00 & 5.60 & 8.60 & 10.60 & 16.60 \\
 \frac{1000v}{K B^\frac{3}{2}} & 120.00 & 100.00 & 81.00 & 88.00 & 74.00 & 63.00 & 57.00 & 96.00 & 92.00 & 88.00 & 8.00 \\
\end{array} \]

The value of \( K \) given for H is one calculated in accordance with my contention that the ionic velocity hitherto assigned to H, namely, 318, ought to be replaced by an unexceptional value, 67.5. For H the value of \( \frac{1000v}{K B^\frac{3}{2}} \) is the largest in the list. Hence, even if the H ion does not give up its charge to nerve, as suggested above, it must exercise the largest depressing effect through its electric force. Ac-

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\(^1\) Sutherland: Philosophical magazine, 1904 [6], vii, p. 402; or Australian association for the advancement of science, 1904, x, p. 122.
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cording to the above list Cs ought to have the smallest depressing
effect and Rb ought to come next. But Mathews found Rb to have
the smallest depressing effect, although expecting Cs to give it. He
quotes Grützner as having found Cs to be less depressing than Rb.
Evidently the point requires further experimental investigation. Next
to Rb in low depressing power and nearly equal come Na and Ba in
the above list, as Mathews found them. Then come K and NH$_4$
nearly equal to Sr, in accordance with experiment. The list makes
Li a rather decidedly stronger depressant than K and NH$_4$, whereas
we saw above that it comes out about equal to them in the experi-
ments. Mg and Ca appear to depress a little more than Sr, while
experiment makes all three about equal. The striking point about
the theoretical measure \( \frac{v a^2}{K d^2} \) for the depressing power of a positive
ion equivalent is that it contains \( v \), the valency. In view of this
fact and the considerable range in the values of K and of B, it seems
to me that the theory gives an adequate qualitative account of the
electric action of positive ions on nerve. As to a complete quantita-
tive test of the theory we are confronted with the difficulty that we
do not know the relation between magnitude of electric force and
amount of stimulation. If the depressing powers of Na and K ions
are as 2.5 to 4.6, it would seem that depressing power is proportional
to excess of electric force over some lower limit which just fails to
stimulate.

We can apply a rather searching test to the foregoing theory by
using it to calculate the amount of electricity available in the experi-
ments of Mathews with solutions for comparison with the directly
determined charge of negative electricity necessary to stimulate
nerve. Weiss has shown$^1$ that to produce stimulation of a nerve a
certain minimum quantity of electricity is required. For the sciatic
of a frog he found this to be of the order $10^{-9}$ coulomb, which is equal
to 3 C.G.S. electrostatic units. Consider now a solution such as that
of sodium chloride which Mathews found to stimulate frog's nerve
at concentration 58.4/12 gms. per litre. In a solution of concentra-
tion 58.4 gms. per litre there are as many molecules of NaCl as there
are molecules of H in 2 gms. of hydrogen, or $88 \times 10^{22}$. Thus a solu-
tion of NaCl of strength 58.4/12 contains $7 \times 10^{19}$ ions of Cl per c.c.,
so that we may take a square centimetre of nerve section immersed
in such a solution to be in contact with $17 \times 10^{12}$ ions of Cl. But the

$^1$ Weiss: Comptes rendus, 1901, cxxii, p. 1068.
electron charge of each ion is $3 \times 10^{-10}$ electrostatic C.G.S. units. So the total charge of the Cl ions in a cm$^2$ is $51 \times 10^2$. By measurement I have found the sectional area of the sciatic nerve of a medium-sized frog to be 0.0038 cm$^2$, while the sum of the sectional areas of the axis cylinders in it is 0.002 cm$^2$. Hence the total charge of the Cl ions in contact with the cross section of all axis cylinders in frog's sciatic nerve in Mathews' experiments with $\frac{m}{12}$ solutions is $10$ C.G.S. electrostatic units. A fraction of this, namely, about $\frac{4}{5}$, is made ineffective through being neutralized by the depressing effect of electric force from the Na ions, so that we deduce 7 units as the stimulating minimum. The agreement in the order of magnitude of the 7 deduced from Mathews' experiments and the approximate 3 determined directly by Weiss is quite satisfactory, and furnishes substantial confirmation of the contention that the stimulation of nerve by solutions must be regarded as a surface action at the cross section of the nerve.

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