NERVE IMPULSE

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Transactions of the Second Conference
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Editor
DAVID NACHMANSOHN

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Second Conference on Nerve Impulse

JOSIAH MACY, JR. FOUNDATION CONFERENCE PROGRAM

FRANK FREMONT-SMITH
Medical Director

IT GIVES ME great pleasure to welcome you to the Second Conference on Nerve Impulse.

The regular members who form the nucleus of this group are already well acquainted with the nature and purpose of the Foundation's Conference Program, but for the benefit of the guests present I would like to take a few minutes to outline what it is that the Foundation hopes to accomplish by these meetings.

We are interested, first of all, in furthering knowledge about nerve impulse, and to this end you have been brought together to exchange ideas, experiences, data, and methods. In addition to this particular goal, however, there is a further, and perhaps more fundamental, aim which is shared by all our conference groups. This is the promotion of meaningful communication between scientific disciplines.

The problem of communication between disciplines we feel to be a very real and a very urgent one, the most effective advancement of the whole of science being to a large extent dependent upon it. Because of the accelerating rate at which new knowledge is accumulating and because discoveries in one field so often result from information gained in quite another, channels must be established for the most relevant dissemination of this knowledge.

The increasing realization that nature itself recognizes no boundaries makes it evident also that the continued isolation of the several branches of science is a serious obstacle to scientific progress. Particularly is it so in medicine that the limited view through the lens of one discipline is no longer enough. For example, today medicine must be well versed in nuclear physics because of the tracer techniques and the injury which can result from radiation. At the other extreme, medicine is certainly a social science and, through mental health, must be concerned with economic and social questions. The answer, then, is not further fragmentation into increasingly isolated specialties, disciplines, and departments, but the integration of science and scientific knowledge for the enrichment of all branches. This integration, we feel, can be encour-

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aged by providing opportunities for a multiprofessional approach to given topics.

Although the fertility of the multidiscipline approach is recognized, adequate provision is not made for it by our universities, scientific societies, and journals. And perhaps, if we are honest, we must admit the presence of other hindering factors. Partly semantic in nature, they may also to some degree be psychological. Admittedly, it is oftentimes difficult to accept data derived from methods with which one is unfamiliar. By making free and informal discussion the central core of our meetings, we hope to achieve an atmosphere which minimizes as much as possible these emotional barriers.

Thus, our meetings are in contrast to the usual scientific gatherings to which you are accustomed. They are not designed to present neat solutions to tidy problems but to elicit provocative discussion of the difficulties which are being encountered in research and practice. For this reason, we ask that the presentations be relatively brief and that emphasis be placed on discussion as the heart of the meeting. Our hope is that the participants will not come prepared to defend a single point of view but will take advantage of this meeting as an opportunity to speak with representatives of other disciplines in much the same way that they would talk with their own colleagues in their own laboratories.

We have, now, thirteen groups functioning under the Conference Program. The following topics are covered: adrenal cortex, aging, biological antioxidants, blood clotting, blood pressure, connective tissues, consciousness, cybernetics, infancy and childhood, liver injury, metabolic interrelations, nerve impulse, and renal function. When a new conference is organized, the Chairman, in consultation with the Foundation, selects fifteen scientists to be the nucleus of the group, and every effort is made to include representatives from all pertinent disciplines. From time to time new members are added by the group to fill gaps in viewpoint or technique. A limited number of guests are invited to attend each meeting, but, for the purpose of promoting full participation by all members and guests, attendance at any meeting is limited to twenty-five. It is inevitable that in no topic can we possibly include more than a small fraction of the key investigators in the field, and one of the difficulties in forming a group like this is that it is necessary to leave out so many people whom we would like to include.

As you know, the transactions of these meetings are recorded and published. This is done because the Foundation, in addition to its interest in the problem of communication between scientists, believes that conveying to those in other fields who are concerned with science the essential nature of scientific research is also an important problem in communication. Logic is a vital aspect of science, but equally essential

is the intuitive or creative aspect. In my opinion, research is as creative as the painting of a portrait or the composing of a symphony. Although logic is, of course, necessary in order to rearrange, to test, and to validate, research thrives on creativity which has its source in unconscious, nonrational processes. Unfortunately, however, in the finished products which we present to the world through our research reports this integral part of scientific endeavor is shriveled by the cold, white light of logic. By preserving the informality of our conference in the published transactions, we hope to give a truer picture of what actually goes on in the minds of scientists and of the role which creativity plays.

From what I have said it must be apparent that these conferences and the published transactions are an experiment. You are a part of that experiment, and the success of it will be measured by how much you, as a participant, gain from the conference. We hope that at this meeting you will feel the freedom inherent in the scientific method, and that if means occur to you by which we may improve our conference procedure you will share them with us.

IONIC PROBLEMS

HENRY B. STEINBACH
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FOR THOSE of you who do not know my major interests, let me explain that I have been interested primarily in problems of ion transport which is probably related to nerve action; there is, however, no definite proof of the relationship at present.

On thinking over the general topic, it seemed to me that it might be wise to start the discussion, by limiting it to the effects of ions upon excitatory and conduction phenomena, and for the moment, rule out some of the more complex features of the action of the nervous system, especially the so-called integrative actions. Even so the effects of ions could include a variety of things. Perhaps of the greatest interest, as far as I am concerned, are the effects of ions upon various physical parameters, such as the electrical characteristics of the nerve axon, thresholds and various similar items. Then probably related to them, but considerably more complex, are the effects of ions upon rhythmically discharging systems, their actions in inducing spontaneous, sometimes rhythmic, activity.

I took the opportunity to go back over some of the literature, and I came to a few conclusions regarding the effects of ions on peripheral nerve and the theories derived from these effects. Those very general conclusions, with which you may not agree, are: a) nerve physiologists have made no major contributions to concepts or theories concerning this problem; and b) nerve, and especially peripheral nerve, is the worst possible material to work on to study fundamental excitation phenomena. The usual form of nerve is made up of delicate strands of axoplasm that presumably do the work, all gummed up with lipid material. The whole seems to resemble a submarine cable where the wire is covered by large envelops of secondary importance. I wonder how much the properties of the axoplasm may be hidden by the extraneous structures; there is no proof one way or the other. There is virtue it seems to me in studying excitation, not nerve.

Also, I think it is apparent, if you look over the literature of the last fifty years, that starting in the mid-1920's and going up to the mid-1940's, there has been a very great preoccupation with measuring ma-

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chines rather than with biological phenomena. There is a recrudescence in interest in the biological phenomena in the last few years, but during the interim period, I think you could almost draw a graph showing an inverse relation between the number of units of machinery and the biological interests of the results.

The usual method of studying the effects of ions is to put the biological material into solutions containing the agents in which one is interested and to note the effects. Under these conditions the actions observed may be subdivided into two types: first, those effects of the ions which are due in some way to their movement and their diffusion properties into or out of the system; and second, the effects of these agents which are actually due to a combination of some sort, implying a rather specific chemical combination with the plasmic substance itself, either the cell membrane or something fairly close to it. This latter process, in a sense, is akin to what the physiologist calls assimilation. So I think there may be two general types of effects that one might expect of any agent applied from the outside, one effect because the material goes in, and another one because a specific chemical reaction takes place.

Whichever of these two categories one adopts, ultimately the effects must be attributed to some of the physical properties of the ions. I, therefore, collected from various chemistry and physics handbooks a few parameters that might be of interest. (Table I)

Looking through the biological literature, there is evident an overpreoccupation with the items in the first column. (Table I) headed Radius - Hydrated Ion. These radii are derived directly from conductance measurements, so where you say radius of hydrated ion, it could just as well be . . .

TABLE I

Parameters of Structure and Properties of Cations of Biological Interest.

	Radius Hydrated Ion Å	Radius Crystal Å	Molar Refraction Gas ml.	Ionic Potential Charge/Radius	Dissociation Constants* Polyphosphate
K	1.98	1.33	2.25	0.75	0.5
Na	2.56	0.96	0.47	1.0	0.05
Li	3.09	0.61	0.08	1.6	0.035
Ca	(4.8)	0.99	1.40	1.9	10^{-6}
Mg	(5.2)	0.65	0.26	3.1	10^{-6}.
Cl	1.93	1.81	9.06		

*Dissociation constants from van Wazer and Campanella (1). Other figures from standard sources.

Shedlovsky: I should like to register, just for the record, a protest against a definite radius of an hydrated ion. That is not operational; it cannot be measured.

Steinbach: I was about to register the same sort of protest. The only meaning that I could ascribe to a "hydrated radius" is that that is the size that a sphere would have if it moved that fast under a given potential gradient through a solution of that viscosity. Is that correct?

Shedlovsky: If Stokes' law held.

Steinbach: That is right, if it were a perfect sphere and were being dragged through a solution under a specified potential gradient with an observable velocity, then it would have that size. Does that fit your objection? There is no more reality than that.

Shedlovsky: Right.

Steinbach: It is, however, the one parameter of ions which I think you will find most referred to in biological literature. Would you agree with that?

Shedlovsky: I would agree with that. I think it would be better, and it would serve all the purpose that this hydrated radius could serve, simply to give the ionic conductance.

Steinbach: In a sense, the figures of the next column (Table I— Radius Crystal) have a little more reality, but even there it is not too good. These radii represent, in essence, factors determining the closest distance of approach, or the stable distance apart, of atoms inside of a crystal. Even here we deal with rather nebulous figures, and when you are operating with ions or atoms at the surface of a crystal or at any other surface, then these figures become a little meaningless.

The next column of Table I gives molar refraction data. Molar refraction is used widely in permeability literature as an index of volume, and in general there is a parallelism between the cube of the radius and the molar refraction. These molar refraction data have been used in biological literature primarily with non-electrolytes and not so much with ions. The main reference I have seen to them in the literature of physical chemistry is with respect to what is called polarizability of an ion, which is an expression of the development of asymmetry between the net negative charge and the net positive charge of an ion. The extent to which you can develop that asymmetry is expressed as polarizability which in turn is roughly parallel to the molar refraction of the substance as a gas.

Another characteristic which is useful to consider is an invented parameter called the ionic potential, (charge divided by radius). With the application of the so-called Fajan's rules, ionic potential seems to be a fairly good index of the extent to which an ion will be bound into a given large polarizable anion. Would someone care to amplify that?

Shedlovsky: I would prefer to consider, rather, the field strength on the surface of an ion, and this, of course, is very closely related to it. For the force by Coulomb's law, take the crystallographic size, put a unit charge of no dimension on the surface, and then divide by the square of the radius. It would be this column divided by the radius again.

In this connection, I should like to point out that H^+, what many chemists call an hydrogen ion, is proton and not hydrogen ion. Let us make a computation. The radii that we see here are all of the order of an Angstrom unit. Order of magnitude is all we are interested in here. The proton has a radius less than 10^{-4} of that value, which means that the field strength of a proton at its surface, if you can speak of it, is of the order of a hundred million times that value, or more. The proton, obviously, cannot very long exist free in any solution or in any material medium containing dipoles or anions. I bring this up at this point because I want to say something about the unique nature of this particular beast a little later on in this discussion.

Wald: May I ask a question that arises from Dr. Shedlovsky's remark? When the proton attaches, as it might frequently do, to a water molecule to form H_3O^+, I take it that the positive charge is distributed over the entire complex.

Shedlovsky: The water molecule is an oxygen ion with two protons on it not diametrically opposed, because if it were, there would be no dipole, and the dielectric constant of water would be around 2 instead of around 80. In fact the angle is not 180° but nearer 120°. However, when another proton comes in and attaches itself, the most stable configuration seems to be a symmetrical distribution of the three protons with equal angles. If you like, you can have them smear around statistically in this manner.

Wald: But in a sense, for the purposes that Dr. Steinbach wants to deal with, we can consider this very peculiar property which you mention, the enormous ratio of charge to area, as being so to speak dispersed; and this brings it a little more into the conventional realm, does it not?

Shedlovsky: May I also call your attention to the following: The oxygen atom, or the hydroxyl group, in crystals has a radius of 1-1/3 Å, like potassium. Now, the addition of another proton does not contribute very much to size. We could expect the hydrogen ion, which is H_3O^+, to have a conductance similar to potassium ion. At 25° in water, that would be about 75 conductive units. The value is 350. That is an interesting anomaly.

Steinbach: The last column in Table I illustrates the next generalization I am about to make. In dealing with complex formation, in

general the order of strength with which an ion is bound in a complex is directly related to this ionic potential or any other comparable parameter that you want to put down. These figures are taken from a paper by van Wazer and Campanella (1) dealing with a polyphosphate. They measured, by a slightly indirect method, dissociation constants of this polyphosphate complex with the different ions I have listed there. I have rounded these figures out a little, since some variability was noted.

You will see that potassium with its low ionic potential has a dissociation constant of about 0.5. Sodium, with a higher ionic potential, is much lower in dissociation constant. Lithium is somewhat lower, and then you get into the small, compact, double-charged ions like calcium and magnesium. There is a difference between those two, but I just rounded both out to about 10^{-6} to show you they were several orders of magnitude different from the alkali metal ions. I have a strong suspicion that the properties of ions which are reflected in these varying dissociation constants of the polyphosphates are of considerably more importance to cells than are the abilities of the ions to move freely through an aqueous solution.

Since we are biologists and are visually minded, Figure 1 shows some ionic dimensions drawn to scale and a diagram illustrating how ionic potential might influence strength of binding of ions on a deformable surface.

Those sizes imaginary or not, are the order of magnitude of size that one tends to deal with in thinking of diffusion problems, and you can see the effects of this calculated value of hydration size.

For reasons touched by Dr. Shedlovsky, I left out hydrogen and hydroxions.

Shedlovsky: Let us make it like potassium.

Steinbach: It would be about that. 'If, now, ions were acting in a stimulatory process whereby they were actually combining with some constituent in the surface, magnesium could be pictured as pretty tightly held into that surface and calcium a little less so (Figure 1). The ion would be, so to speak, sticking out a little. Sodium would be sticking out quite a bit, and potassium sticking out even more, indicating a much looser attachment.

That is just a general picture of the way in which you might visualize these ions as having effects of two definite kinds. On the one side, their contribution to a diffusion process would be roughly measured by the outer circles of the hydrated ions. Their contribution toward fitting tightly into some surface structure in the cell, or at the surface of the cell, would be illustrated roughly by the attachment of magnesium, calcium, sodium, and potassium.

Shedlovsky: May I mention at this point an additional fact? We
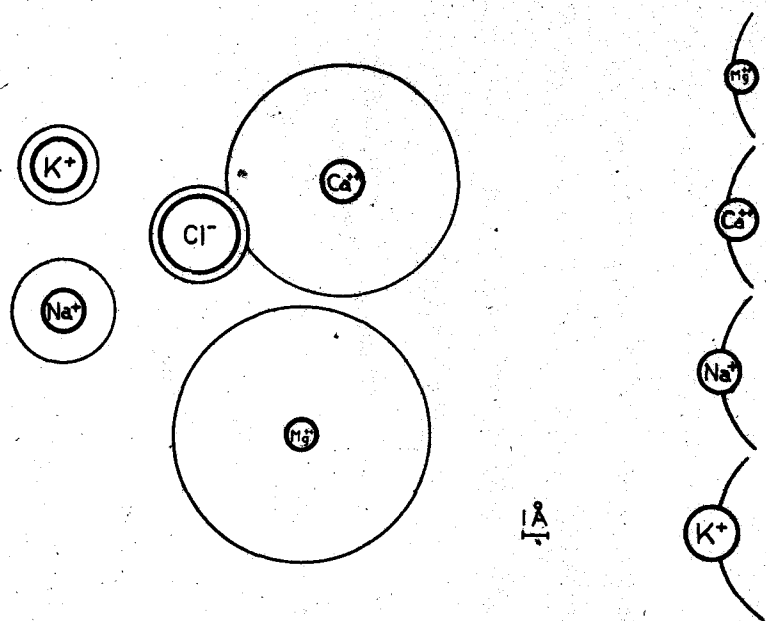
DIFFUSION   **COMPLEX FORMATION**

FIGURE 1. Crystal radii of ions (heavy circles) and hydration shells (light circles) on the left. Scale (1Å) in center. At the right, ions are pictured as held to a deformable surface. The simple assumption was made that penetration of the surface was for a fixed distance per unit charge.

notice here that the size, which is derived from conductance for the positive ions, runs roughly inversely to the crystallographic size. The smaller they are the bigger they are, so to speak. It is not a linear relationship, but not a bad one. It is rather curious on the other hand, that for the negative ions, chloride, bromide, iodine, half sulphate, and so on, all have conductances of 70-odd conductance units.

Steinbach: In general, with the anions of that nature, the so-called crystal size is larger than the comparable cations, and hence it follows the degree of hydration—whatever that means—is less. Is that not true, roughly?

Shedlovsky: Yes, but if you try to apply the same argument for hydration of the negative ions that you do for the positive, you encounter trouble. A fairly good rough rule is to consider normal negative ions of about the conductance of potassium.

Steinbach: In addition to these features, there are, of course, chemical