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The Nobel Prize in Physiology or Medicine 1936

- Sir Henry Hallett Dale
- Otto Loewi

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Natural or artificial stimulation of nerves gives rise to a process of progressive excitation in them, leading to a response in the effector organ of the nerves concerned.

Up until the year 1921 it was not known how the stimulation of a nerve influenced the effector organ's function, in other words, in what way the stimulation was transmitted to the effector organ from the nerve-ending. In general it was thought that it came about through direct transmission of the stimulation wave from the nerve fibre to the effector organ. But the possibility of transmission by chemical means had also been considered and experiments had been conducted on these lines. As a result of his own experiments, Howell[1] had come to believe that vagus stimulation released potassium in the heart and that this was the cause of the resultant effect, and Bayliss[2] discussed the possibility, in view of the similarity in action of the so-called vagomimetic substances and chorda stimulation, that this stimulation might be caused by the production of such substances. Although these data were known to me, my attention was only drawn years after my discovery to the fact that earlier (in 1904 to be exact) Elliott[3], in the last paragraph of a short note, suggested the possibility that the stimulation of sympathetic nerves might be brought about by the release of adrenaline, and that Dixon[4] had already communicated experiments in an inaccessible site to test whether, during vagus stimulation, a substance was released which contributed to the stimulation reaction.

In the year 1921 I was successful for the first times in obtaining certain proof that by stimulation of the nerves in a frog's heart substances were released which to

some extent passed into the heart fluid and, when transferred with this into a test heart, caused it to react in exactly the same way as the stimulation of the corresponding nerves. In this way it was proved that the nerves do not act directly upon the heart, but rather that the direct result of nerve stimulation is the release of chemical substances and that it is these which bring directly about characteristic changes of function in the heart.

It was, of course, possible right from the start that this mechanism which I described at the time as “humoral transference”, but which is now known as “chemical” transference as the result of a well-founded suggestion by H.H. Dale, does not represent an isolated phenomenon but a special condition which also appears elsewhere. We shall soon see that this supposition was justified. But before I go into that I should like to characterize in more detail the substances which are released by nerve stimulation and produce the effect. First of all, I must mention my distinguished collaborators E. Navratil, W. Witanowski, and E. Engelhart, and thank them.

Let me begin with the transfer medium of the reaction in vagus stimulation which I have called “vagus substance”. We were able to determine that its effect is inhibited by atropine[5] and very quickly disappear[6]. In looking for a substance with both these characteristics, I found that out of a series of the known vagomimetic substances, muscarine, piloearpin, choline, and acetylcholine, only the last-named possessed them[7]. We were then able to establish further that the rapid disappearance of the action of the vagus substance and acetylcholine (Ac.Ch.) through the breaking down of these substances was caused by the action of an esterase in the heart[6], which had already been postulated by Dale[8]. I was able to show furthermore that the action of this esterase could be specifically inhibited through minimum concentrations of eserine[7]. This discovery was important not only because, for the first time, the operational mechanism of an alkaloid had been revealed, but especially because the discovery enabled the theory of the chemical transference of nerve stimulation to be developed for the first time. On the one hand, this eserine action provided a means of revealing the minimal quantities of Ac.Ch. being released by nerve stimulation which would otherwise, because of their rapid destructibility, have remained undisclosed. On the other hand, we are able, in cases where for any reason it is technically impossible or difficult to prove directly the release of Ac.Ch. in nerve stimulation, to draw the conclusion indirectly from the increase in effect of nerve stimulation after previous eserination that the nerve stimulation is being produced by the release of Ac.Ch.

And now we must return to the characterization of the vagus substance.

The vagus substance behaves identically with Ac.Ch. not only in regard to its reaction to atropine, and to its destructibility with esterase but also concerning all other characteristics. As Dale and Dudley[9] were able to produce it directly from the organs, there can be no more doubt that the vagus substance is Ac.Ch. and in future I shall refer to it as such.

As regards the character of the substance which is released through stimulation of the sympathetic nerves of the heart and other organs, I was able to show earlier that it shares many properties with adrenaline; both, for example, are destroyed by alkali[20] and by fluorescence and ultraviolet light[6], the activity of both is abolished by ergotamine[21]; on the other hand, as Cannon and Rosenblueth[10] have shown, it is raised by small and in themselves ineffective quantities of cocaine, the adrenaline-sensitizing action of which Fröhlich and I[11] found some 25 years ago.

Like the effect of adrenaline, an equal effective strength of the sympathicus substance declines very slowly in the heart, much more slowly incidentally than might have been expected in view of the rapid oxidizability of adrenaline or sympathicus substance in vitro. The cause of this, as revealed by Dr. Ralph Smith of Ann Arbor and me in a series of specially conducted experiments not as yet published, turns out to be the giving off of substances from the heart which inhibit adrenaline oxidation. There must, of course, be some physiological purpose in the fact that individual devices exist, on the one hand to remove the acetylcholine as quickly as possible and the adrenaline, on the other hand, as slowly as possible. And now we must return to the chemical nature of the sympathicus substance.

Although for some time it had been considered probable after all we had seen that the sympathicus substance was adrenaline, I was only able to give direct proof of it this year. Gaddum and Schild[13], on the basis of a statement by Paget, investigated the significance of a green fluorescence visible in ultraviolet light which pointed to adrenaline in the presence of O_2, and alkali, and found that this appears to a high degree specific for adrenaline. I was now able to show that not only the heart extract, but also the heart fluid, shows this reaction after accelerated periods of stimulation[12]. Accordingly I consider it proved that the sympathicus substance is adrenaline.

Now I must briefly consider the question of to what extent the neuro-chemical mechanism, that is to say the chemical transference of nerve stimulation, is important other than to the heart.

Firstly, Rylant[14] and others were able to show that with warm-blooded animals too, vagus stimulation released Ac.Ch. which was responsible for the resultant stimulation reaction. I must mention in this connection that my collaborator Engelhart[15] was able to show, in accordance with the well-known fact that the heart vagus in warm-blooded animals ends at the auricular/ ventricular boundary, that here considerably more Ac.Ch. was to be found before and after stimulation in the auricle than in the ventricle, whereas in a frog's heart, where the vagus extends over the ventricle as well, the distribution of Ac.Ch. over auricle and ventricle is even. As the heart vagus belongs to the parasympathetic system, the question had to be examined whether and to what extent the neurochemical mechanism applied here. The first investigation on this point also came from my Institute, from Engelhart[16] , who was able to prove the release of Ac.Ch. as a result of stimulation of the oculomotor nerve. The total result of the many different, resultant investigations on various organs can be summarized by saying that up until now no single case is known in which the effect of the stimulation of the parasympathetic nerves was not caused by the release of Ac.Ch.

As, to my mind, a lecture should concern itself not only with results, but also with still open questions, I must touch on the following: As all activity caused by the application of Ac.Ch. can be halted by atropine, one might expect that wherever Ac.Ch. is released as a result of nerve stimulation, the effect could everywhere be halted by atropine. This, however, is not so. Contractions of the bladder after stimulation of the pelvic nerve, dilation of the vessels of the salivary gland after stimulation of the chorda nerve still occur even after atropinization. And here we must mention the following strange observation by V.E. Henderson[17]: he found that after preliminary atropinization, vagus stimulation in the intestine produced no increase of tonus, but an increase of peristaltic contractions. The reason for these remarkable exceptions has so far escaped us.

The neurochemical mechanism is everywhere apparent in the field of activity of the parasympathetic system, as in the sympathetic system. But we have Dale[18] and his collaborators to thank for the recognition that the stimulation of certain nerve fibres which belong anatomically to the sympathetic system lead to the release, not

of adrenaline, as in the overwhelmingly large number of cases, but of Ac.Ch.

To sum up then, it may be said that the neurochemical mechanism applies in the stimulation of all autonomic nerves.

But it also embraces a much wider area. We owe this knowledge in the main to the basic investigations of Dale. There is no need, therefore, for me to go further into this in my lecture.

We now have to discuss the important question of whether the nerve stimulation influences only the function of the effector organ by the release of nerve substances, as I will call the chemical transmitters for the sake of briefness, or whether it perhaps exerts another influence as well.

Here we shall be well advised to take as a starting-point the mechanism of action of atropine or ergotamine. With Navratil[19] I was able to show (and this finding was confirmed many times over) that these alkaloids do not, as had been thought previously, attack and incapacitate the nerves themselves. We were able to show this by demonstrating that even after using atropine and ergotamine, nerve stimulation still released nerve substances. This shows that atropine and ergotamine do not impair the function of the nerves, which is a liberating one, that is to say, they do not paralyse the nerves, but exert an antagonistic influence on the action of the substances produced. By recognizing that after previous application of atropine or ergotamine the stimulation of the respective nerves is known to have no effect at all upon the effector organ, it has been proved that nerve stimulation has no other effect but to release nerve substances. What other kind of function can remain for the nerve if the action of the substance released coincides absolutely with the effect of the nerve stimulation? Although what follows is self-explanatory, I still think it desirable to state it expressly: in all cases in which the neurochemical mechanism occurs, the nerves only control function to the extent of the release of the substance: the place where this occurs is in the effector organ of the nerve. From then onwards, the released substance exerts control: the functioning organ is, therefore, *its* effector organ exclusively.

And now we must consider in which directions our knowledge of the physiological process has been extended, beyond what we have already said, by the discovery of the neurochemical mechanism.

There will be no cause for argument if we see the most importance in the fact that at last a clear answer has been found to the age-old question as to the nature of the stimulus-transfer from nerve to effector organ.

Next in importance appears to me to be the explanation of the nature of the peripheral inhibition. Up until now, it appeared quite inconceivable that the stimulation of a nerve could lead to inhibition in the effector organ. With the proof that this inhibition comes about because the nerve releases a function-inhibiting substance, the reason for it becomes clear. At the same time, however, something else is proved which seems to me to be of great importance: the release of a substance by the nerves is the expression of a positive function, an activation. This proves that the *direct* effect of the stimulation of all nerves, whether activating or inhibitory, represents a promotion of function, for this is what the release of the substance does.

Today, because we know how it happens, this solution strikes us as self-evident. For, since the process of stimulation is, to a certain degree, unspecific and furthermore interference in stimulus frequencies which certainly form the basis of some inhibitory manifestations in the animal region of the central nervous system cannot, in the case of peripherally inhibitable organs, be regarded as the cause of inhibition, I see no other possibility, at least in general, as to how nerve stimulation can lead to inhibitions of the effector organ at all than by chemical means; in other words, the chemical mechanism is the only conceivable way.

So much for the field of activity and the importance of the neurochemical mechanism.

After this description which touches upon the general nature only of the neurochemical mechanism, we will now consider more exactly its finer mechanism.

First of all the question arises: where are the substances released by nerve stimulation localized, or, in other words, where is the point of attack of the nerve stimulation? A priori, two possibilities exist: the substances are released in the nerve endings or in the effector organ. Investigations of this question carried out so far are concerned only with Ac.Ch.

For the time being we shall only draw upon findings which concern the Ac.Ch. content of organs after nerve degeneration.

As far back as 30 years ago, Anderson[22] observed the following: after degenerative division of the oculomotor nerve, light stimulation was for a long time without effect, regardless of whether the eye had been eserinized or not. There followed a period when light stimulus was still ineffective to the uneserinized eye, but not to the eserinized eye. At this moment, as could be shown, a weak regeneration of the oculomotor nerve had begun. In Anderson's time it was not possible to give an adequate explanation of these findings. Today, when we know that oculomotor stimulation releases AC.Ch., the action of eserine is revealed as being simply to increase the effect of the Ac.Ch. by inhibiting that of the esterase, and Anderson's results become absolutely clear. With degeneration of the oculomotor nerve the Ac.Ch. disappears. Eserine then also becomes ineffective. With the start of regeneration of the oculomotor nerve the Ac.Ch. appears again, but in too small quantities to cause miosis with light stimulus alone, i.e. without the increased activity provided by eserine. Thus Anderson's experiments provide the first proof that the existence of Ac.Ch. in the eye is dependent upon the nerves. Later Engelhart[16] in my own Institute produced this proof in a direct manner. With direct Ac.Ch. determination he found that after degeneration of the oculomotor nerve in corpus ciliare and iris, the Ac.Ch., present in considerable quantities in preserved nerves, completely disappears. This shows that, in many organs at any rate, the Ac.Ch. content and its maintenance is connected with the presence of the nerve. There are two possible explanations for the disappearance of the Ac.Ch. after nerve degeneration. Either the Ac.Ch. is a part of the nerve and disappears then naturally with its degeneration, or it belongs to the effector organ. Then we should have to assume that the formation and maintenance of the Ac.Ch. amount in the effector organ was, in some mysterious and trophic manner, dependent upon the nerve, so that it would disappear with its degeneration. Should the Ac.Ch. be a product of the effector organ and not the nerve ending, then, according to Dale, it would have to disappear, after degeneration, through some kind of atrophy. This hypothesis would then require a further subhypothesis, that of separate and specific transmission system in the effector organ quite unlike any other. This assumption would be necessary, because, after oculomotor nerve degeneration, the effector organs, corpus ciliare and iris do not degenerate, and yet the Ac.Ch. disappears. The influence of the oculomotor nerve degeneration must, in that case, only extend to the mysterious transmission system. In respect of these difficulties alone, a far likelier assumption is that the Ac.Ch. which is

released by nerve stimulation belongs to the neurone itself, or more exactly to the nerve ending. There is in my opinion, in at least one instance, compelling proof for the correctness of this supposition.

In Dale's Institute, Feldberg and Gaddum[23] have shown that stimulation of the preganglionic sympathetic fibres in the neck releases Ac.Ch. in the sup.cerv. ganglion, which itself stimulates the ganglion, so that progressive stimulation is set up in the postganglionic fibres. In elegant experiments directed towards the question of the localization of the release of Ac.Ch. in the ganglion, Feldberg and Vartiainen[24] were recently able to prove that it was released neither by the preganglionic fibres nor by the ganglion cells themselves, the only direct effector organ. They concluded, therefore, that the Ac.Ch. was produced in the synapse. Synapse is not an anatomical but a purely functional concept. It indicates the spot where the nerve ending comes into contact with the cell, and has been adopted by histologists only in this sense. If, therefore, it can be proved that Ac.Ch. is formed in the "synapse", it can only, in my opinion, be in the preganglionic nerve ending or in the ganglion cell. As the ganglion cell can be ruled out, as Feldberg and Vartiainen have shown, there only remains, it appears to me, the nerve ending as the site of release. Although proof of this has so far only been obtained directly in the case of preganglionic sympathetic endings, there is, nevertheless, much to make us think that in other places as well the nerve substances are released in the nerve endings themselves. We know that in many organs by no means each single, functioning unit is accorded a nerve fibre. At most, according to Stöhr, one occurs for every hundred capillaries. When the nerve is stimulated, however, all react. In these cases, how does the nerve substance diffuse to those regions without nerves? I believe that the nerve ending is here the liberation centre. This supposition is supported when we consider that when the autonomous nerves are stimulated the two same substances are always released in very different organs having a quite different chemical structure and accordingly undergoing quite different chemical changes. If the substances were not being released in the nerve endings, but peripherally of them, then we should again have to assume the presence of some mysterious mechanism capable of transferring the stimulation of the nerve ending to the supposed peripheral position where the substance would be released; in which case, the discovery of the neurochemicalmechanism would not, in my opinion, represent any important progress.

We come now to the next question concerning this delicate mechanism.

So far we have only spoken of the release of the substance from the nerve ending. This is only to say that a free nerve substance emerges from the nerve ending. But it is important for an understanding of the nature of nerve function to know what exactly we should imagine is implied by this release. A priori the following possibilities exist: either the substances are not present in the nerve ending when the nerves are in a state of rest and are only formed by nerve stimulation and, once formed, diffuse, or they are already present in the state of rest, but can only diffuse after stimulation. As regards the formation of nerve substances through the nerves, it is certain that this can be done. Even Witanowski[25] in his day found Ac.Ch. in the vagus, in the sympathicus and in the sympathetic ganglia. The last two findings were confirmed by Chang and Gaddum.[26] As Ac.Ch. is not present in the blood, it cannot diffuse from there, and neither, on account of its ready destructibility, could it diffuse from elsewhere in the nerves and ganglia. The same applies for adrenaline. Recently we have succeeded in showing the presence of adrenaline in a frog's brain in a state of rest or even anaesthetized, and also in the upper cervical ganglia of cattle. It was characterized by its effect upon the heart which was similar to that of adrenaline, through the neutralizing of this effect by ergotaminization and also by its destructibility through fluorescent light. These findings, therefore, confirm that the nerve substances are formed by the nerve and are present even in a state of rest. Whether the nerve, when stimulated, produces further substance as well is another still undecided question which we are not touching upon here. However interesting in itself the answer to this question may be, it does not appear to me to be of essential importance, since the basic effect of nerve stimulation is the release of the substances. There are two possibilities as regards the processes of release and diffusion: either the substances are present in a free and diffusible state in the nerve ending, but the nerve ending when in a state of rest is impermeable and only made permeable to them after stimulation, when they become diffusible and effective, or, the substances in the resting state are in some way combined and indiffusible and only the stimulation releases the combination and thereby makes them diffusible and effective. If the first possibility were to apply, then we must not find the Ac.Ch. at all, since, as has been shown, esterase is found everywhere in the nerves and this, as we shall soon see, destroys the free Ac.Ch. But we do find it in the nerve. This fact alone suffices to show that it is not present in a free, diffusible state in the nerve ending. In addition, Bergami[28] recently found, in confirmation of earlier experiments by Calabro[27], that Ac.Ch. only issues from the free end of severed nerves if the nerve is stimulated. In this case, the release cannot, of course, be attributed to any change in the state of permeability brought about by stimulation, since the free

nerve ending has no membrane. The second possibility which I mentioned earlier must apply, namely that the Ac.Ch. in the unstimulated nerves is bound in some way and thereby protected from the assault of the esterase. In fact, it is present in such quantity in hearts where there is no vagus stimulation, that in a freely diffusible state it would be more than sufficient to stop the heart altogether. On its own it is ineffectual and is protected against the action of the esterase, in contrast to when it is in a diffusible state.

In experiments directed towards the study of this question Engelhart and I[29] found the following: If one determines the initial value of Ac.Ch. in a heart section, leaving the remaining portion of the heart intact for a few hours, as much Ac.Ch. is found in it afterwards as in the beginning. Dale and Dudley, incidentally, found the same in the case of the spleen. In an organ in a state of rest, therefore, the Ac.Ch. is protected against the esterase. But if free (that is to say diffusible) Ac.Ch. is added to a heart in a state of rest, it is destroyed. All this goes to show that obviously, as Dale also assumed, the Ac.Ch. is present in the organ in a state of rest in some kind of loose, non-diffusible combination, and for that reason it is non-susceptible to attack by esterase and non-effective. Such combinations we know do very often occur in an organism. The so-called “vehicle function” of the blood implies in fact no more than the ability of the blood’s component parts to bind substances and, when necessary, to release them. But the binding must in any case be a very loose one, as after destroying the structure, for instance by mincing the organ, the Ac.Ch. is very quickly destroyed by esterase. Nerve stimulation would accordingly appear to have the effect of releasing from this combination the Ac.Ch. which has been proved to be present in the nerve.

The same applies also for the nerve substance in the sympathetic system, adrenaline. As I was able to show this year[12], the heart contains 1 gamma to 2 gamma per gram, which corresponds to a concentration of 1:1 million to 1:500,000. Whereas adrenaline added to the heart will already be effective in a concentration of 1:100 million to the maximum, the concentration of 100-200 times more adrenaline in a heart in a state of rest will be without effect. Therefore it also must be present in some kind of inactive combination in the heart. This fact also seems to me to be of importance in the possible interpretation of certain other findings. It is known that in many organs the adrenaline action is quickly over. Up until now this has been explained by the speedy oxidation of adrenaline. This is certainly the case for pure adrenaline solutions *in vitro*. *In vivo*, on the other hand, adrenaline is not only not easily oxidized, but all the organs contain

substances – among them, as has been proved, amino acids – which, even in minimal quantities, have a direct inhibiting effect upon the oxidation of adrenaline. How then does this rapid cessation of activity come about? It may, in part, be due to counteractions. In some cases, however, the disappearance of activity could be due to rapid transference of the adrenaline into an ineffective linkage as is to be found in the heart.

Now let us return from this digression to the subject of the release of the nerve substances. This occurs very quickly and the action of the released nerve substance is very rapid also, although between release and effect the diffusion process has also to be set in motion. The time interval varies in length in different cases, but is in part certainly dependent upon the distance of the releasing nerve ending from the effector cell. According to Brown and Eccles[30] this is 80-100 omega in the case of the heart, but only 2 omega in the ganglionic synapse. This must mean that release coincides with stimulation. Dale is able to explain quite easily the fact that the effect reaches the ganglion cell almost without any time lapse by the fact that the release in the nerve ending occurs directly with contact with the ganglion cell, whereas in the heart, where incidentally the first contraction after vagus stimulation is smaller, a certain time is required for diffusion to the effector cells. As in the case of release and effect, the speed with which the substance and with it the effect disappears, varies in different objects. The discovery of the chemical mechanism of the effect of vagus stimulation in the heart was only possible because in this case the destruction of the Ac.Ch. occurs so slowly that the substance had time to diffuse, in sufficient quantity to be active, into the heart; in the ganglia on the other hand, the destruction occurs so rapidly that the Ac.Ch. in the perfusion fluid is only demonstrable after preliminary eserination. The differences in time between freeing and disappearance in both cases are easily understandable if we consider the quite different purposes which the nerve stimulation serves in both these cases.

And now, finally, we come to the localization of the point of attack of the nerve substances.

As long as it was not known that the autonomic nerves, when stimulated, release substances which condition the successful effect of the nerve stimulation, it was assumed in general, in consideration of the fact that the action picture of the so-called vago- and sympathico-mimetic substances is identical with the

stimulating of the corresponding nerves, and, further, with the fact that it was believed that the alkaloids, atropine, and ergotamine, which inhibit the action of the substances, paralyse the corresponding nerves, that the vago- and sympathico-mimetic substances stimulate the nerves somewhere peripherally. But as they are effective even after nerve degeneration, it was assumed, with justification at the time, that a non-degenerative myoneural junction was the point of attack. Today, now that we know that the nerves do release nerve substances, this view is no longer tenable. The nerve substances, considered as vago- or sympathico-mimetic substances, would have to act like these, that is to say, they would have to stimulate the myoneural junction and release substances, etc. on their own. In this case there would be no kind of effect upon the effector organ. Quite apart from this, the supposition that the nerve substances stimulate the nerve somewhere is quite superfluous by the proof shown above, that the alkaloids atropine and ergotamine which inhibit the activity of the vago- and sympathico-mimetic substances, do not, as was supposed, paralyse the nerves, but are simply antagonistic to the substances. If all this is evidence against the nerve as point of attack, it has also been proved that Ac.Ch. and adrenaline are also effective in the absence of nerves. Ac.Ch., for instance, dilates vessels which are not parasympathetically innervated. Adrenaline increases the activity of the still nerveless embryonic heart and stimulates the arrectores pilorum, which, according to Stöhr, are also nerveless, etc. Therefore, the point of attack of the nerve substances must be some part of the effector organ itself, probably chemical or chemico-physical in character and not morphological.

As Dale has proved, we can no longer say that the nerve substances reproduce the action picture of the nerves but rather it is a fact that the nerves reproduce the action picture of the substances, since they release these and thus lead to effective action. That the activity caused by any one nerve substance appears principally at the spot where it is released, that is to say, that in that particular spot the cells are receptive to its action, is a local phenomenon of the specific sensitivity to certain chemical substances which is met with everywhere in the living organism and which is Erie of the foundations of its function and, therefore, of its very existence and which can only be understood teleologically and not causally; think, for example, of the finely graduated, specific sensitivity of the respiratory centre to CO_2.

Up until now we have discussed only the effect of the nerve substances on the organ in which they are released through nerve stimulus. Are they only active

there, or in other distant organs too? We have already mentioned that a part of the released substance diffuses into the blood or into some other perfusing fluid. This could present the possibility of its action being extended to other more distant organs. What is the position here? Given special conditions, which I would like to characterize as pathological, this could happen.It has been proved that when the breaking up of the Ac.Ch. by an esterase, is inhibited by eserine, the Ac.Ch. penetrates with the blood to other organs in sufficient quantities to cause activity. Furthermore, Cannon[31] by preliminary sensitizing of organs through denervation, or cocainization, made them so hypersensitive to the sympathicus substance that they reacted to its release in any organ. In the same way as in these experimentally induced disturbances, it could also happen perhaps that in cases of illness, the release of surplus quantities of substance or incomplete destruction may interrupt the normal release and destruction, leading to hypersensitivity of organs and the appearance of effect at a distance. It would be very desirable if in future clinicians would give consideration to these relationships with a view to explaining certain symptoms and groups of symptoms which until now, partly without sufficient foundation, have been considered as purely reflex. Under normal conditions, however, the effect of the nerve substance would be limited to the organ in which it is released. The hormones are there to exert a general control, that is to say not a localized chemical one, on the organs.

In conclusion a word or two on the question of how the neurochemical mechanism fits into the connecting pattern of cells. With the discovery that its influence comes about through substances which are released by the nervous system itself, we have the first proof that the nervous system is not only an effector organ for chemical influences from outside, and not only a participant in general metabolism, but that it has itself a specific chemical influence upon happenings in the organism. On closer examination this is not surprising.

In nerve-free multicellular organisms, the relationships of the cells to each other can only be of a chemical nature. In multicellular organisms with nerve systems, the nerve cells only represent cells like any others, but they have extensions suited to the purpose which they serve, namely the nerves. Accordingly it is perhaps only natural that the relationships between the nervous system and other organs should be qualitatively of the same kind as that between the non-nervous organs among themselves, that is to say, of a chemical nature.

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