Nobel Lecture

Nobel Lecture, December 12, 1936

Some Recent Extensions of the Chemical Transmission of the Effects of Nerve Impulses

The transmission of the effects of nerve impulses, by the release of chemical agents, first became an experimental reality in 1921. In that year Otto Loewi published the first of the series [1, 2, 3, 4, 5, 6] of papers from his laboratory, which, in the years from 1921-1926, established all the principal characteristics of this newly revealed mechanism, so far as it applied to the peripheral transmission of effects from autonomic nerves to the effector units innervated by them. Of the general history of this discovery, of the speculations which preceded it, and of its more recent developments in detail in many laboratories, as regards one aspect of it particularly by Cannon and his co-workers in Boston, you have heard from Professor Loewi himself. I propose to deal with a wider application of this conception of chemical transmission, which has resulted from researches carried out during the past three years in my own laboratory, by a number of able investigators - J.H. Gaddum, W. Feldberg, A. Vartiainen, Marthe Vogt, G.L. Brown, Z.M. Bacq. These investigations have made it possible to suggest that a fundamentally similar chemical mechanism is concerned in the transmission of excitatory effects at the synapses in all autonomic ganglia, and at the motor nerve endings in ordinary, voluntary muscle.

You will see that, according to this relatively new evidence, a chemical mechanism of transmission is concerned, not only with the effects of autonomic nerves, but with the whole of the efferent activities of the peripheral nervous system, whether voluntary or involuntary in function. This extension of the principle of chemical transmission has come as a surprise to many; the relative ease, with which the evidence justifying it can be obtained, has been surprising to ourselves. But the basic conception, which encouraged us to undertake experiments in this direction, was no novelty to me; and for its origin I must ask you to look briefly at some experiments which I had already made and published in 1914[7] . My chemical collaborator at that time, Dr. Ewins[8], had isolated the substance responsible for a characteristic activity which I had detected in certain ergot extracts, and it had proved to be acetylcholine, the very intense activity of which had been observed by Reid Hunt[9] already in 1906. Since we had found this substance in nature, and it was no longer merely a synthetic curiosity, it seemed to me of interest to explore its activity in greater detail. I was thus able to describe it as having two apparently distinct types of action. Through what I termed its "muscarine" action, it reproduced at the periphery all the effects of parasympathetic nerves, with a fidelity

which, as I indicated, was comparable to that with which adrenaline had been shown, some ten years earlier, to reproduce those of true sympathetic nerves. All these peripheral muscarine actions, these parasympathomimetic effects of acetylcholine, were very readily abolished by atropine. When they were thus suppressed, another type of action was revealed, which I termed the "nicotine" action, because it closely resembled the action of that alkaloid in its intense stimulant effect on all autonomic ganglion cells, and, as later appeared, on voluntary muscle fibres. I am tempted here to quote some words which I wrote in that paper, in 1914.

"It is clear, then, that the distinction between *muscarine* and *nicotine* activity cannot be made with absolute sharpness... Nor is there any evidence enabling us to regard one group of the molecule as responsible for the one type of action, and another for the other. One can merely conclude that there is some degree of biochemical similarity between the ganglion cells of the whole involuntary system and the terminations of voluntary nerve fibres in striated muscle, on the one hand, and the mechanism connected with the peripheral terminations of craniosacral involuntary (i.e. parasympathetic) nerves on the other."

In the same paper I had speculated on the possible occurrence of acetylcholine in the animal body, and on its physiological significance if it should be found there; and had pointed out the extraordinary evanescence of its action, suggesting that an esterase probably contributed to its rapid removal from the blood.

When, therefore, some seven years later, Loewi described his beautiful experiments, showing that stimulation of the vagus nerve produced its inhibitor effects on the frog's heart by the liberation of a chemical substance; and when his successive papers provided cumulative evidence of the similarity of this substance to acetylcholine, including its extreme liability to destruction by an esterase, which Loewi extracted from the heart muscle; I believe that I was more ready than most of my contemporaries for immediate acceptance of the evidence for this "Vagusstoff", and more eager, almost, than Professor Loewi himself, to assume its identity with acetylcholine. There was wanting, it seemed to me, only one item of evidence to justify certainty as to the nature of this substance, namely, a proof that acetylcholine itself, and not merely some choline ester of closely similar properties, was an actual constituent of the animal body.

Professor Loewi has already mentioned the extraction and identification of acetylcholine, as a natural constituent of a mammalian organ, by my late and deeply lamented colleague, H.W. Dudley, and myself[10], in 1929. He has also dealt with the general rule that parasympathetic effects are transmitted by acetylcholine, and true sympathetic effects by what his own most recent experiments appear definitely to identify as adrenaline. He has mentioned also the important exceptions to that rule. In view of such exceptions, it seemed to me desirable to have a terminology enabling us to refer to a

nerve fibre in terms of the chemical transmission of its effects, without reference to its anatomical origin; and, on this functional basis, I[11] proposed to refer to nerve fibres and their impulses as "cholinergic" or "adrenergic", as the case might be. Such a functional terminology seemed to me the more important, in view of the evidence which was already coming from our experiments, that acetylcholine had a much wider function as a transmitter of nervous excitation, than that concerned with the post-ganglionic fibres of the autonomic system, and their effects on involuntary muscle and gland cells. For all such effects of acetylcholine, directly analogous to those which Loewi discovered in relation to the heart vagus, were covered by what I had termed the "muscarine" action of acetylcholine, and were all very readily suppressed by atropine. But there remained, as yet without any corresponding physiological significance, the other type of action of acetylcholine, so similar in distribution to that of nicotine, which had come to my notice nearly twenty years earlier. Was it credible, I asked myself, that this sensitiveness of ganglion cells, and of voluntary muscle fibres, to the substance now known to be the transmitter of peripheral parasympathetic effects, was entirely without physiological meaning? I could not believe it. At the same time, it had to be recognized that the transmission of nervous excitation at ganglionic synapses, and at motor nerve endings in voluntary muscle, was a phenomenon of a different order from any of those in connexion with which the intervention of a chemical transmitter had hitherto been demonstrated, or even considered. Acetylcholine, released at the peripheral endings of the vagus or the chorda tympani, could be pictured as reaching the heart cells or those of the salivary gland by diffusion, and there inhibiting an automatic rhythm, or exciting glandular secretion. At a ganglionic synapse or a motor ending on a voluntary muscle fibre, on the other hand, the evidence was clear, that a single impulse, reaching the end of the preganglionic or motor nerve fibre, caused the passage from the ganglion cell, along its post-ganglionic axon, of a single nerve impulse, and no more; or caused the passage, from the motor end plate of the muscle fibre, of a single wave of excitation, of propagated contraction, and no more. In both cases, the phenomenon had the appearance of a direct, unbroken conduction, to ganglion cell or muscle fibre, of the same propagated wave of physico-chemical disturbance as had constituted the preganglionic or the motor nerve impulse, with only a slight, almost negligible retardation in its passage across the ganglionic synapse or the neuromuscular junction. And, indeed, such continuity of the conduction, in both cases, had generally been assumed, and, in the case of the neuromuscular conduction, in particular, had been implicit in the interpretation of a great body of detailed evidence, which the ingenuity and the labours of two generations of physiologists had produced.

Could the stimulating action of acetylcholine on ganglion cells and on muscle fibres, its "nicotine" actions, be pictured as intervening in these rapid and strictly limited transmissions of excitation across ganglionic and neuro-muscular synapses? We could only imagine such intervention, if we could think of acetylcholine as appearing and disappearing in a manner entirely different from that involved in its transmission of peripheral parasympathetic effects. We must suppose that an impulse, arriving at the ending of a preganglionic or a voluntary motor nerve fibre, releases with a flashlike suddenness a small charge of acetylcholine, in immediate contact with the ganglion cell or the motor end plate of the muscle fibre. We must suppose that this sudden rise in

concentration of acetylcholine stimulates the ganglion cell to the discharge of a postganglionic impulse, or initiates a propagated wave of excitation along the muscle fibre. And we must suppose, further, that the acetylcholine then disappears with a suddenness comparable to that of its liberation, so that it has vanished by the end of the brief refractory period of the ganglion cell or the muscle fibre, which is thus left fully responsive to another discharge of acetylcholine, by another nerve impulse. Such a sequence of events seems to involve two things. The first is a depot, closely related to the preganglionic or motor nerve ending[12], in which acetylcholine may be held in some association which prevents its action and protects it from destruction, and from which it can be immediately liberated by the arrival of a nerve impulse. Professor Loewi has mentioned the evidence for such storage of acetylcholine, waiting for liberation, at parasympathetic nerve endings; and Brown and Feldberg[13], in my laboratory, have obtained evidence that nearly the whole of the acetylcholine, obtainable by extraction from a normal sympathetic ganglion, disappears when the preganglionic nerve fibres are caused to degenerate by section; so that its maintenance is, in fact, dependent on the integrity of the preganglionic nerve endings. The second thing required, by the suggested action of acetylcholine in transmitting the kind of excitation we are discussing, is a mechanism for its very rapid removal, so that it disappears completely within the few milliseconds of the refractory period of muscle fibre or ganglion cell. One naturally thinks of the specific cholinesterase, first detected by Loewi in heart muscle, and since found to be widely distributed in the blood and tissues. Even when obtained in solution this potent enzyme destroys acetylcholine with a quite remarkable rapidity; and if we could suppose it to be concentrated on surfaces at preganglionic or motor nerve endings, in immediate relation to the site of liberation and action of acetylcholine, it might furnish an adequate mechanism for the complete destruction of this substance, even during the very brief interval of the refractory period. Here, again, I am permitted to make preliminary mention of experiments which Dr. Franz Briicke, who earlier worked under Prof. Loewi, is even now making in my laboratory, and which have already given uniform evidence that a large amount of cholinesterase is present in a sympathetic ganglion, and that this, like the acetylcholine obtainable from such a ganglion, disappears largely when the preganglionic fibres, and their endings in the ganglion, are caused to degenerate. We have evidence, then, that both the reserve of acetylcholine, and the esterase required for its destruction, are in fact associated with the preganglionic nerve endings, as our hypothesis demands. I am departing, however, too far from the true historical order, and presenting recent and confirmatory details of evidence, before I have described the initial observations, which opened this new field to our experimental exploration.

Although from the time when it first became clear that Loewi's Vagusstoff was acetylcholine, I had begun to consider the possible significance of its "nicotine" actions, it was long before the possibility of its intervention as transmitter at ganglionic synapses, or at voluntary motor nerve endings, seemed to be accessible to investigation. Experiments on the ganglion came first in order. Chang and Gaddum[14] had found, confirming an earlier observation by Witanowski, that sympathetic ganglia were rich in acetylcholine. Feldberg, just before he returned to my laboratory for a stay of some years, had observed, with Minz and Tsudzimura[15], that the effects of splanchnic nerve

stimulation are transmitted to the cells of the suprarenal medulla by the release of acetylcholine in that tissue. Now these medullary cells are morphological analogues of sympathetic ganglion cells, and Feldberg, continuing this study in my laboratory, found that this stimulating _ action of acetylcholine on the suprarenal medulla belonged to the "nicotine, side of its actions. Clearly we had to extend these observations to the ganglion; and a method of perfusing the superior cervical ganglion of the cat, then recently described by Kibjakov[16], made the experiment possible. Feldberg and Gaddum[17], though unable to reproduce effects obtained by Kibjakow with pure Locke's solution, found that, when eserine was added to the fluid perfusing the ganglion, stimulation of the preganglionic fibres regularly caused the appearance of acetycholine in the venous effluent. It could be identified by its characteristic instability, and by the fact that its activity matched the same known concentration of acerylcholine in a series of different physiological tests, covering both "muscarine" and "nicotine" actions. It appeared in the venous fluid in relatively high concentrations, so strong, indeed, that reinjection of the fluid into the arterial side of the perfusion caused, on occasion, a direct stimulation of the ganglion cells. It was clear that, if the liberation took place actually at the synapses, the acetylcholine liberated by each preganglionic impulse, in small dose, indeed, but in much higher concentration than that in which it reached the venous effluent, *must* act as a stimulus to the corresponding ganglion cells. Feldberg and Vartiainen[18] then showed that it was, in fact, only the arrival of preganglionic impulses at synapses which caused the acerylcholine to appear. They showed, further, that the ganglion cells might be paralysed by nicotine or curarine, so that they would no longer respond to preganglionic stimulation or to the injection of acetylcholine, but that such treatment did not, in the least, diminish the output of acetylcholine caused by the arrival of preganglionic impulses at the synapses. There was, in this respect, a complete analogy with the paralysing effect of atropine on the action of the heart vagus, which, as Loewi and Navratil had shown many years before, stops the action of acetylcholine on the heart, but does not affect its liberation by the vagus impulses.

My colleagues have added other chapters of interest to this story of chemical transmission at the synapses in the ganglion. I may just mention Brown and Feldberg's[13] observation that potassium ions, the mobilization of which is so intimately connected with the nervous impulse, will liberate acetylcholine from its depot in the ganglion, in a manner closely recalling the effect of preganglionic impulses; and their more recent finding[19] that, with prolonged preganglionic stimulation, the ganglion sheds into the fluid perfusing it several times as much acetylcholine as can be obtained from a similar, unstimulated ganglion by artificial extraction. The effects of eserine, on the transmission of excitation in the ganglion, are complicated by a paralyzing action of this alkaloid on the ganglion cells, and still need further elucidation. I can more usefully pass to our recent work on voluntary muscle, in which such effects are much clearer.

The difficulty facing us in the case of the voluntary muscle was largely a quantitative one. In a sympathetic ganglion, the synaptic junctions, at which the acetylcholine is released by the incident preganglionic impulses, form a large part of the small amount of tissue perfused. In a voluntary muscle the bulk of tissue, supplied by a rich network of capillary blood vessels, is relatively enormous in relation to the motor nerve endings, of

which only one is present on each muscle fibre. The volume of perfusion fluid necessary to maintain functional activity is, therefore, relatively very large, in relation to the amount of acerylcholine which the scattered motor nerve endings can be expected to yield when impulses reach them. With the skilled and patient co-operation of Dr. Feldberg and Miss Vogt[20], however, it was possible to overcome these difficulties, and to demonstrate that, when only the voluntary motor fibres to a muscle are stimulated, to the complete exclusion of the autonomic and sensory components of the mixed nerve, acetylcholine passes into the Locke's solution, containing a small proportion of eserine, with which the muscle is perfused. If, by calculation, we estimate the amount of acetylcholine thus obtained from the effect of a single motor impulse, arriving at a single nerve ending, the quantity is of the same order as that similarly estimated for a single preganglionic impulse and a single ganglion cell; in both cases 10^{-15} gram, which corresponds to about three million molecules of acetylcholine. We found that, if the muscle was denervated by degeneration, direct stimulation, though evoking vigorous contractions, produced no trace of acetylcholine. If, on the other hand, the muscle was completely paralysed to the effects of nerve impulses by curarine, stimulation of its motor nerve fibres caused the usual output of acerylcholine, though the muscle remained completely passive. Again there is a complete analogy with Loewi's observations on the heart vagus and atropine.

With this demonstration, that acetylcholine was liberated at the endings of motor nerve fibres in voluntary muscle, in immediate relation to the motor end plates of the muscle fibres, only one side of our problem had been solved. Acetylcholine, injected into the vessels of a ganglion, could be shown to stimulate the ganglion cells to the discharge of postganglionic impulses. In the case of normal voluntary muscle, on the other hand, the evidence before us suggested only that certain muscles of frogs, reptiles and birds responded to the application of acetylcholine, not by quick, propagated contractions like those evoked by motor nerve impulses, but by slow, persistent contractures, of low tension. As for the normal muscles of mammals, on which our evidence of acetylchohne liberation had been obtained, these were supposed, on evidence provided by myself among others, to give no response at all to acetylchohne, except in large doses, and then only irregularly. The denervated mammalian muscle was known to be highly sensitive to acetylcholine, but the evidence, again from myself among others, suggested that its response was of the nature of a contracture, and not of a quick, propagated contraction.

Considering the manner in which acetylcholine must reach the motor end plates of the muscle fibres, if it were indeed the transmitter of motor nerve excitation - that it must appear with a flash-like suddenness, in high concentration, simultaneously at every nerve ending - we concluded that the ordinary method of injecting acerylcholine, so that it reached the muscle by slow diffusion from the general circulation, could not possibly reproduce this abrupt appearance at the points responsive to its action. We attempted a nearer approach to these supposed conditions of its natural release, by a method which enabled us, after a brief interruption of the arterial blood supply, to inject a small dose of acetylcholine, in a small volume of saline solution, directly and rapidly into the empty blood vessels of the muscle[21]. The responses which we thus obtained were of an entirely different kind from any which had previously been recorded. A dose of about 2 gamma of acetylcholine, thus injected at close range into the vessels of a cat's gastrocnemius,

produced a contraction with a maximal tension equal to that of the twitch produced by a maximal motor nerve volley, and of a rapidity but little less than that of the motor nerve twitch. We have direct evidence that only a small part of the acetylcholine so injected actually reaches the muscle end plates by diffusion from the vessels; and we argued that, in any case, it could not reach them simultaneously, but only in rapid succession; so that the response, in spite of its superficial resemblance to a rather slow twitch, must actually be a brief, asynchronous tetanus. My colleague, G.L. Brown, using a strictly localized electrical lead from the muscle, involving only a few fibres, has obtained clear evidence that the response has, indeed, that nature. It is a brief burst of unsynchronized and repetitive responses of the individual muscle fibres; but these individual responses are, without doubt, quick, propagated contractions, and there is no semblance of contracture about the phenomenon. Unlike the response of the denervated muscle to acetylcholine, this quick response of normal mammalian muscle is suppressed with great ease by curarine.

At this point I must briefly refer to some observations made only in the past few weeks, and still in progress. The normal mammalian muscle had seemed to present us initially with the greatest difficulty, being supposed not to react to acetylcholine at all. This difficulty being removed by a more adequate technique, we had to face the fact that the function of acetylcholine, as transmitter of voluntary motor nerve impulses, could not be confined to the case of mammalian muscle. The muscle of the frog, the classical object of innumerable studies of neuromuscular conduction, had been found to respond to acetylcholine, indeed, but only by contractures of low tension, and not by propagated contractions comparable to those evoked by nerve-volleys. Here again, we reflected that the method which had been used for the application of acetylcholine, the immersion of the excised muscle in a suitable dilution of the substance, could hardly be expected to reproduce that rapidity of access to the appropriate points on the fibres, which its simultaneous liberation at all nerve endings would achieve. The patient skill of my colleague, G.L. Brown, has now made it possible to apply acetylcholine to the frog's muscle by direct injection of a small dose into its empty blood vessels, in a manner quite analogous to that which produced such significant results in the mammalian muscle. If 1 gamma of acetylcholine, for example, dissolved in 0.1 cc of Ringer's solution, is thus injected suddenly into the artery supplying the frog's gastrocnemius, the surface of the muscle, covered with its glistening aponeurosis, shows immediately the ripple and shimmer of innumerable, unsynchronized contractions, propagated along the fibres and fascicles of the muscle; at the height of the effect a tension of several hundred grams is developed; and the electrical record gives decisive evidence that this response is an irregular, asynchronous tetanus, and not a contracture. With larger doses this tetanus is cut short and extinguished by the contracture - the only effect of acetylcholine on frog's muscle which earlier work had recognized.

From the study of the mammalian muscle we have also obtained what seems to be clear evidence concerning a mechanism by which acetylcholine, suddenly liberated at the nerve ending to transmit the excitatory effect of a motor impulse to the muscle fibre, may, with a comparable suddenness, be removed completely during the refractory period. If this removal is due, as we have suggested, to the destructive action of cholinesterase,

concentrated on surfaces at the nerve ending, we should expect that eserine, with its depressant effect on the action of the cholinesterase, discovered by Loewi and Navratil, would delay the disappearance, from the neighbourhood of the motor end plates of the muscle fibres, of the acetylcholine liberated by a single nerve volley, and would thereby modify the response of the muscle. The effect is easy to demonstrate. Eserine causes, in fact, a great increase of the maximum tension attained by the contraction of the muscle in response to a maximal nerve volley. The all-or-none principle forbade us to suppose that such a potentiated response was a single twitch; and the electrical records showed that it was, indeed, repetitive, and had the nature of a brief, diminishing tetanus[21].

The eserine has so depressed the action of the esterase at the nerve endings, that the acetylcholine liberated by a single nerve volley lingers there, and reexcites the muscle at each emergence from successive refractory periods, until the concentration falls at last below the stimulation threshold. Bacq and Brown[22] have more recently extended these observations to a series on artificial eserine analogues, and have found that the potentiating action on the response of mammalian muscle to single nerve volleys is, in fact, proportional, in the different compounds of the series, to the anticholinesterase action, as independently determined.

There are many other aspects of these phenomena, some of them still under active investigation in my laboratory. I must be content today to have presented the main headings of the evidence, which, as it seems to me, is forcing upon us the conclusion, in spite of the preconceptions which made the idea initially so difficult to entertain, that acetylcholine does actually intervene as a chemical transmitter of excitation, in the rapid and individualized transmission at ganglionic synapses and at the motor endings in voluntary muscle; that, in the terminology which I have proposed, the preganglionic fibres of the autonomic system, and the motor nerve fibres to voluntary muscle, are also "cholinergic".

You will see that we are thus led to the conclusion that nearly all the efferent neurones of the whole peripheral nervous system are cholinergic; only the postganglionic fibres of the true sympathetic system are adrenergic, and not even all of these. As I have earlier pointed out, on more than one occasion[12, 23], before the evidence for the cholinergic function of voluntary motor nerves was nearly as strong as it has now become, this new classification of nerve fibres, by chemical function, renders at once intelligible the formerly puzzling evidence as to the functional compatibility of different types of nerve fibre, in replacing one another in experimental regeneration. The whole of the evidence of such replacement, obtained by Langley and Anderson early in the present century, can now be summarized by the simple statement that any cholinergic fibres can replace any other cholinergic fibres, and that adrenergic fibres can replace adrenergic fibres, but that no fibre can be functionally replaced by one which employs a different chemical transmitter. The chemical function, as I have expressed it, seems to be characteristic of the neurone, and unchangeable. In that connexion, particular interest appears to me to attach to the recent observations of Wybauw[24], which seem to provide clear evidence that

the antidromic vasodilatation, generally believed to be produced through peripheral axon branches from sensory fibres, also employs a cholinergic mechanism. If this is substantiated, and if my suggestion holds good that the chemical mechanism is characteristic of the neurone, the question at once presents itself, whether at transmission of excitation will be found.

Hitherto the evidence concerning a chemical transmission in the central nervous system, of the type which we have found prevailing at all peripheral synapses, is scattered and insufficiently uniform in its indications. The basal ganglia of the brain are peculiarly rich in acetylcholine, the presence of which must presumably have some significance; and suggestive effects of eserine and of acetylcholine, injected into the ventricles of the brain, have been described. I take the view, however, that we need a much larger array of well authenticated facts, before we begin to theorize. It is here, especially, that we need to proceed with caution; if the principle of chemical transmission is ultimately to find a further extension to the interneuronal transmission in the brain itself, it is by patient testing of the groundwork of experimental fact, at each new step, that a safe and steady advance will be achieved. The possible importance of such an extension, even for practical medicine and therapeutics, could hardly be overestimated. Hitherto the conception of chemical transmission at nerve endings and neuronal synapses, originating in Loewi's discovery, and with the extension that the work of my colleagues has been able to give to it, can claim one practical result, in the specific, though alas only short, alleviation of the condition of myasthenia gravis, by eserine and its synthetic analogues.

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