# The Nobel Prize in Physiology or Medicine 1936

# Presentation Speech

Presentation Speech by Professor G. Liljestrand, member of the Staff of Professors of the Royal Caroline Institute, on December 10, 1936

Your Majesty, Your Royal Highnesses, Ladies and Gentlemen.

In the second book of his famous work on the history of Rome, Livy has described how Menenius Agrippa, sent out by the Senate to attempt to bring about a reconciliation with the Plebeians who were on strike, told them the fable of the revolt of the limbs against the stomach, stressing the necessity of the cooperation of all parts in the interest of the whole. This cooperation, or «consensus partium», described here in a simple form, is the main objective of physiological research. To a large extent it is brought about by the body fluids and especially by the blood. These not only effect the necessary distribution of the supply from outside, but also the removal of waste products; the intensive research done today on internal secretions has also shown how important it is that the various hormones should be distributed by this means, from the organs in which they are produced to other parts of the body. Characteristic of the whole pattern of this cooperation, either humoral or chemical, is the fact that it is established relatively slowly but extends over a considerable time. Simultaneously also, another mechanism is set up, through the development of the nervous system, which permits the exchange of rapid messages and their swift transposal into action. Occasionally such messages are sent out through an act of will which brings the skeletal muscles into action. But our inner organs also are under the influence of the nervous system. The heart beats which are accelerated by work and mental emotion, the pupils which contract when light enters the eye, and the gastro-intestinal canal which, through its movements, dispatches food according to its kind are examples of how activity adapts itself to the influence of certain nerves which, in these instances, are not under the command of the will. In this portion of the nervous system, then, there is a kind of self-government and it is therefore known as the autonomic nervous system. This is composed of two main parts, which are both of equal importance, but which to a certain extent represent conflicting interests. Taking the heart as an example, one section, the so-called sympathetic system, conveys those impulses which accelerate beating, while the parasympathetic system on the other hand conveys those which have a slowing-down effect.

If external work has to be performed, or if dangers threaten, then the sympathetic part of the autonomic nervous system takes over the direction and develops increased activity. The heart pumps more blood, the muscles are put into a state of defence and receive an extra supply of fuel, while, at the same time, there is a momentary cessation of activity in a variety of other places, for instance in the movements of the intestinal canal. In contrast, different activity occurs in the parasympathetic system as local conditions require, for instance in the function of a single organ.

It was generally thought that impulses in the nerves act directly on the muscles or glands bringing about a change in their activity. But as early as 1904, Elliott presented a different interpretation. From the medulla of the adrenal glands, which, as embryonic development shows, is related with the sympathetic nervous system, a substance can be produced, i.e. adrenaline, the effect of which is remarkably similar to that produced by increased activity in the sympathetic system. Elliott therefore supposed that the impulses in the sympathetic nerves produced a release of adrenaline in the nerve endings which would then be the real vehicles of the stimulation effect. Ten years later, Dale published a comprehensive investigation of another substance, acetylcholine, for which he found a corresponding conformity with the effect of the parasympathetic stimulation. As, however, at that time acetylcholine had not been met with in the body, there was not sufficient basis for a discussion as to whether it normally transmitted impulses.

While the idea that nerve stimulation could be brought about by the release of certain substances was not entirely new, it is nevertheless thanks to Loewi that the idea was brought from the realm of unproven hypotheses on to the firm ground of certain experience. He first used a heart with its nerve trunk, removed from a frog or toad, connecting up the heart chamber with a small glass container in which was a small quantity of a suitable nutrient fluid. If the nerve trunk was stimulated by electrical means, the number and strength of heart beats altered according to circumstances there are, namely, in the nerve trunk fibres from both the sympathetic and the parasympathetic systems. If after such stimulation Loewi transferred the fluid which had been pumped in and out of the heart into another similarly prepared heart, he found that the fluid itself had taken on properties capable of producing changes in the activity of the organ corresponding to those which had earlier been produced by the nerve stimulation. Through this very simple but ingenious experiment it was proved that the nerve stimulus can release substances having the action characteristic for the nerve stimulation and further observations left no doubt whatever that the nerve stimulus itself was passed on to the organ by chemical means.

Painstaking work now began with the object of determining the nature of the substances concerned - it was soon apparent that different substances were involved in the stimulation of the two different kinds of nerves. This task would appear hopeless considering the incredibly small quantities in which the substances are released. Chemical methods alone were of no avail. But Loewi carried out instead a model analysis, using those activities which were obtained in the living organism under changing conditions. With the sympathicus substance he was able to prove in this way that, in a series of important points such as destruction through oxidation and under the effects of certain kinds of irradiation, as well as in regard to its action, it corresponded absolutely with adrenaline. As regards the parasympathetic substance, the task was more difficult on account of its rapid breaking down in the presence of blood and tissue - this supports the contention made previously that the parasympathetic nerves act locally whereas the action of the sympathetic nerves is more widespread. Loewi and Navratil discovered that the breaking down could be prevented by the addition of the vegetable base physostigmine and this made it possible to work out a method which later made the detection of the substance very much easier. After considerable work, Loewi was able to determine the nature of this substance too, and to prove that the parasympathetic substance was identical with acetylcholine.

Loewi's discoveries have successfully withstood the searching test of reexamination. Numerous investigations have shown also that the release of the two substances mentioned is in no way restricted to the nervous system of the heart. Many scientists, notably Cannon, after comprehensive tests, have discovered that adrenaline, or a very similar substance, appears after stimulation of other sympathetic channels. And Engelhart, a colleague of Loewi's, proved the existence of acetylcholine in the anterior chamber of the eye as a result of contraction of the pupil with the entry of light. Corresponding observations were made for many other organs, among others by Dale and his collaborators. Further support for the view that acetylcholine plays a part in the body under physiological conditions was obtained when Dale and Dudley were able to prepare from the body small quantities of this substance.

In recent years Dale and his distinguished collaborators have been able to add to our knowledge of the chemical transmission of stimuli in two extremely important points. In his earlier investigations with acetylcholine Dale was able to observe an effect on the nerve ganglia themselves or on the ganglia of the autonomic nervous system in which a kind of change-over takes place. He was then led to ask whether there could be a conduction of impulses from one nerve cell to another through the agency of acetylcholine. Using an elegant method described by the Russian Kibjakov, Feldberg and Gaddum were able to prove with Dale that acetylcholine appears in the nerve ganglia after stimulation of the connecting nerves. One can appreciate how sensitive the methods used must be when it is realized that only one hundred thousandth (1/100,000) of a milligram of acetylcholine a minute was produced under favourable conditions. The role of acetylcholine as a transmittor is not, however, restricted to the autonomic nervous system. Dale and his pupils proved with great skill that it plays a role in the production of muscular contractions on the part of the motor nerves. On the one hand, the appearance of the substance in connection with the transmission of impulses was confirmed, on the other hand it was also proved that under suitable experimental conditions infinitely small quantities of acetylcholine produced muscle contractions of a corresponding nature.

In understanding the effects of a series of different substances on the organism, the discovery of the chemical transmission of nerve stimuli represents a revolution. A simple and natural explanation is found for the strange conformity between the effect of adrenaline and acetylcholine on the one hand and the stimulation of the sympathetic and parasympathetic systems on the other hand; and the same applies for different substances having a more or less similar effect. But one now has a different point of view with regard to the effect of other substances as well, for example the vegetable bases atropine and physostigmine. Certainly, the observations made have a fundamental significance for our interpretation of the physiological processes of the nervous system, where, in the light of chemical transmission, various so-called summation and inhibitory phenomena can be better understood. Certain observations made during recent years point to practical consequences which will be of value in combating a number of pathological conditions. The importance of any discovery, however, does not only lie in the fact that it brings clarity and understanding to a number of observations not previously understood; it also poses quite new problems and leads research into new channels. The intensive work which is at present being carried out in different laboratories on questions connected with these observations proves convincingly what a stimulating effect the fresh ideas connected with the transmission of nerve stimuli have already had.

Sir Henry Dale, Professor Otto Loewi. The Royal Caroline Institute has decided to award to both of you jointly, this year's Nobel Prize for Physiology or Medicine for your discoveries in respect of the chemical transmission of nerve action. You, Professor Loewi, first succeeded in establishing proof of such transmission and in determining the nature of the effective substances. This work was, in part, built up on earlier research to which you, Sir Henry, made an essential contribution. The results were consolidated and complemented in many important respects by you and your collaborators. You and your school have also greatly extended the range of the new conception by later discoveries. Through these various discoveries, which have stimulated research in innumerable parts of the world, therefore demonstrating once again the international character of science, pharmacology has been very considerably influenced, and physiology or medicine enriched to a high degree.

On behalf of the Staff of Professors, I express to you our heartiest congratulations and hope that it may be granted to you to take part in further research into this new territory for a long time to come. With this hope, I have the honour to ask you to receive the Nobel Prize for Physiology or Medicine from the hands of His Majesty the King.

From *Nobel Lectures*, *Physiology or Medicine 1922-1941*, Elsevier Publishing Company, Amsterdam, 1965