I. INTRODUCTION

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As a professional pharmacologist, it is an honor to be invited to introduce a physiological symposium. This certainly reflects in part an appreciation of the innumerable essential contributions that pharmacology has made to the progress of physiology. In fact, pharmacology started from physiology, used its methods and has as its main goal the revealing of physiological function from the reactions of living matter to chemical agents. The very conception to use drugs as tools in the study of function oriented me towards pharmacology. In 1898, therefore, I joined Hans Horst Meyer and remained with this great master until 1909. During that period, in 1903, in order to improve a little my poor knowledge in physiology, I went to England and studied for a while with such figures as Starling, Bayliss and Barcroft. It was in Starling's láboratory—pardon labóratory—that I had the good fortune to meet an eager young worker; his name was Henry Dale. Our interests and aspirations had much in common and a close mutual relationship immediately started. This soon developed into an intimate personal friendship which ever since—for now fifty years—has enriched my life.

Pharmacology has generously repaid what it owed to physiology. To restrict myself to just a few of the many contributions that pharmacology has made to the subject matter of our symposium, I may remind you that the analysis of the curare effect led to the eventual discovery of the motor endplate as a distinct and important functional unit of striated muscle. The analysis of the nicotine effect led to the discovery of the peripheral ganglionic synapse in autonomic nerves. Recognition of the similarity between the effects of specific chemical compounds with those of stimulation of particular nerves led to the concept and eventually to the proof of the chemical transmission of the nervous impulse.

This may provide some comprehension as to why a pharmacologist was chosen to introduce this physiological symposium. This particular pharmacologist was apparently selected because for decades he has been fairly interested and active in the last mentioned contribution to physiology. The validity of my assumption is strongly supported by the choice of the title of the symposium: "On Neuro-humoral Transmission." The term "neuro-humoral" for many years has been replaced by "neuro-chemical." "Neuro-humoral transmission," however, was the term I selected to christen my baby in 1921.

The discovery proved to be quite a fertilizer and I am thrilled and proud that today, 32 years later, this symposium comes about. To my mind this is a kind of family convention, where three generations: grandfathers—two of them, Sir Henry and I—and perhaps more important, a huge flock of children and grandchildren are happily gathered.

The progress made by the younger generation has been vast. This becomes evident from the magnitude of our program, though it obviously can cover only selected sectors of the field. It may readily be seen why the elucidation of the

kind of mechanism through which nerves act on their effectors has raised an extraordinary interest. Prior to the recognition of neuro-humoral transmission, it had been known for a long time that the nervous system is susceptible to chemical influences. Through the discovery of the chemical transmission of the nervous impulse, it was proven for the first time that the nerve itself exerts specific chemical activities by producing and releasing the agents through which it operates. In retrospect the chemical mechanism of nervous action does not seem surprising; within cell complexes devoid of nervous elements, mutual influences of one cell on another can obviously occur only through chemical events. In principle, the nerve cell is not unlike other cells, although its morphology may be different. From this point of view it was perhaps to be expected that the relationship between nerve cells and other cells would prove to be chemical in nature.

Progress in the field we are concerned with has been and will be made possible in the future by successful search for adequate methods. Scientific ideas deserve this name only if their correctness can be checked by means of appropriate methods. These frequently come up much later and are often, as are genuine concepts, unexpected gifts of our subconscious mind. Trusting therefore that adequate approaches may emerge later, we should not discard our most cherished concepts, but communicate them to others and preserve them, not in our refrigerator, but in our incubator, where in time they may even mature a little. Believe me, when our creative power will be fading one day, we will have to come back to our "canned" ideas. Confidence in their eventual development can be founded on a survey of the history of our own subject. I should like to illustrate this by referring to a few most important steps in it.

First, a former coworker of mine, the late Walter Morley Fletcher, reminded me in 1929 that I had expressed to him a clear idea of the chemical nature of the transmission of the nervous impulse one day in Marburg, back in 1903. Immediately afterwards, however, the idea slipped my mind and came back eighteen years later, when in 1921 a method of checking its correctness occurred to me.

Second, Dale, as early as 1910, noticed some imperfections in the resemblance between the actions of the sympathetic nerves and those of adrenaline, which Elliott in 1904 had suggested as the sympathetic transmitter, and further pointed out the better reproduction of these neural effects by noradrenaline. From that time it took more than thirty years until the discovery by von Euler and Holtz of noradrenaline as the chief transmitter of sympathetic nerve impulses.

Third, there was an interval of about twenty years between Dale's discovery of the activity of acetylcholine at ganglionic synapses and his hunch and ingenious proof that acetylcholine was indeed the transmitter at those synapses and at the neuro-muscular junction.

Anyone who discusses, even in a brief introduction, the problem of chemical transmission of the nervous impulse in general cannot refrain from touching on a most recent development. It concerns the continually recurring question as to the extent to which neuro-chemical transmission may be valid. Results obtained by Eccles in some brilliant recently published investigations brought him to the conclusion that the chemical theory is applicable to the transmission of nerve

impulses not only at the peripheral junctions but also at the synapses within the central nervous system.

We know much less about the mechanism than about the extent of the chemical transmission. I would like to touch on just a few gaps in our knowledge in this respect, in fact on three, and dwell a little on the last.

First: very little is known about the mechanism of the release of transmitters; the only thing we seem to know is that cations play a part as conditioning factor and can act as a trigger mechanism. Progress here may be expected from pharmacological analysis which has successfully started within the last decade.

Second: it is generally accepted that, like most chemicals effective in extremely small amounts, the transmitters combine with specific receptors which, as constituents of the surface-membrane of the effector cells, are links in a functional chain. The nature of this combination is unknown and so is the character of the primary change of the membrane produced by the combination. This results in a change of the polarized state of the membrane and thereby in a change of the functional state of the cell.

Third: not only the character, but also the number of the transmitters released from afferent nerves is uncertain. We know that impulses conducted in different branches of a single afferent fibre, ending synaptically at flexor as well as at extensor motoneurons, excite one and simultaneously inhibit the other. This opposite effect seems to favor the assumption that two different transmitters are involved. On the other hand, it does not *a priori* seem very likely that a single nerve-fibre should release more than one kind of transmitter. The question, in any case, is: can one transmitter agent be responsible for opposite effects on motoneurons and if so, how?

While occupied with this problem, I recalled the impressive results of experiments conducted on spinal dogs, as far back as 1909, by Magnus in Sherrington's laboratory. Strictly localized stimulation of the skin of a limb produced a contralateral extensor reflex if the limb was in passive flexion; it produced a contralateral flexor reflex if the limb was in passive extension. As those reflexes are the result of reciprocal innervation of agonists and antagonists, Magnus' experiments demonstrate that the same afferent stimulus is able to excite as well as to inhibit both flexor and extensor motoneurons. It is most unlikely that these different effects arise from a plurality of transmitters since information does not yet exist to indicate differences in the receptor structure of motoneurons. I therefore am inclined to surmise that only one transmitter of the impulses in afferent nerves of the skin was involved and that the different—in fact opposite—effects, obtained by the same stimulation, were due to different states of the respective motoneurons at the time of stimulation. These differing states of the motoneurons obviously resulted from the postural alterations imposed on the antagonistic muscles prior to the stimulation and were imparted to the motoneurons by impulses in the afferent nerves of those muscles.

Each time I re-read this last paragraph, I had the feeling, which I am afraid you will share, that it might not fit perfectly into the scope of an introductory

address. I could, however, not persuade myself to delete it. I therefore sought an excuse for my stubbornness. Eventually, I found two.

First: an introduction should put the audience into a receptive mood for the coming treat. With part of the audience one may achieve this by offering more philosophical, with another part by offering more factual aspects. This may have induced me to prepare a nice mixture.

Second: as a pharmacologist I like to take advantage of any chance to emphasize the importance of the state of the cells as one of the factors which will determine the nature of their reaction. So far the conditions responsible for and the factors involved in determining the state of the cells are little known. Yet, we are entitled to be optimistic since the interest, especially of neuro- and myophysiologists as well as of neuro- and myopharmacologists, has been increasingly and most successfully concentrated on the properties, functions and reactions of cells. For detailed analysis refined, specific methods were needed and were developed. Many of them are extremely complicated and training is necessary to familiarize oneself with them. This obviously may lead to some methodical specialization and also to some narrowing of the horizon, particularly within an already specialized branch of science.

We often do not know from where fundamental ideas originate. Broad perspective of knowledge, which permits many kinds of associations, at least provides a favorable basic condition for them. The growing recognition of the danger involved in strong specialization has made symposia increasingly desirable. They aim at widening the horizon by offering through personal exchange the opportunity of becoming acquainted with different aspects of and individual views on the subject, its implications and ramifications. Hence everybody should feel free to present his individual observations, criticisms, concepts, interpretations, hypotheses. With well trained people, as we are supposed to be, there is no danger that this "freedom of speech" might degenerate into some kind of mental anarchy.

The introducer would feel more than happy if he has succeeded in creating the right atmosphere.