Nobel Lecture

Nobel Lecture, December 12, 1949

The Central Control of the Activity of Internal Organs

A recognized fact which goes back to the earliest times is that every living organism is not the sum of a multitude of unitary processes, but is, by virtue of interrelationships and of higher and lower levels of control, an unbroken unity. When research, in the efforts of bringing understanding, as a rule examines isolated processes and studies them, these must of necessity be removed from their context. In general, viewed biologically, this experimental separation involves a sacrifice. In fact, quantitative findings of any material and energy changes preserve their full context only through their being seen and understood as parts of a natural order. This implies that the laws governing organic cohesion, the organization leading from the part to the whole, represent a biological uncertainty, indeed an uncertainty of the first order. It becomes all the more acute, the more rapidly the advances of specialization develop and threaten the ability to grasp, or even to appreciate it. While this state of affairs has just been referred to, our subject is defined by its general content. In particular it deals with the neural mechanisms by which the activity of the internal organs is adapted to constantly changing conditions, and by which they are adjusted to one another, in the sense of interrelated systems of functions. It only remains to be added that broadening of our knowledge in these respects is of benefit not only with regard to the human compulsion to understand, but also to the practical healing art. For man also, in health and sickness, is not just the sum of his organs, but is indeed a human organism.

After this short introduction, we now come on to the concrete complex of questions, to which has been devoted the work whose results have earned me this great distinction and have thus brought me into this high circle. The initial situation is defined by the findings, which have now been turned to the common good, concerning the morphological and physical structure of the so-called vegetative - "autonomic" in English usage - nervous system. This was - I believe - a good start, and was brought about by the achievements of the great masters W.H. Gaskell and J.N. Langley, and had been given shape in an easily comprehensible and stimulatingly graphic exposition by the distinguished pharmacologists H.H. Meyer and R. Gottlieb. Of particular interest here in this conception, for which there is good experimental confirmation, is the paired antagonistic innervation of the internal organs, and their grouping according to the separate regions in which the peripheral organization is linked to the central nervous system. (The keywords *sympathetic* and *parasympathetic* characterize the relationships under consideration.) In contrast to the exploration of the vegetative nervous system, which is very far-reaching (even if it is not still without certain inner contradictions) stands a relatively limited understanding of the central organization of the whole mechanism of control. This is not easily understood, because the informative experiments must explore a segment in which elements are also assembled and integrated, which subserve special sensory functions and the movement of the body. Things that are distributed over a wide area in the body itself, lie close together in the central nervous system. Correspondingly an unequivocal differentiation is disproportionately more difficult. The direct contiguity of functionally multivalent pathways and nuclei confuses the experimental elucidation of related symptoms. One thing had nevertheless become clear, namely that the parts of the brain communicating directly with the spinal cord at the upper end - the medulla oblongata, and the segment lying directly beneath the cerebrum, the so-called diencephalon - exert a decisive influence on the vegetative controlling mechanisms. As regards the diencephalon further orientation had been achieved to the extent that it was realized that the parts of it lying nearest the base of the skull, i.e. the *hypothalamus*, were particularly important to the nature of the whole enquiry. Observations at the sickbed in conjunction with what was ascertained in the deceased at autopsy, and in addition experiments which provided some rough pointers, had led to this insight (Karplus and Kreidl *et a*l.). Something which still, however, lay in obscurity, when my own investigations were started, was the allocation of definite functions to particular morphological substrata, was, in other words, the organic structure of the diencephalic vegetative control system. To throw as much light as possible on this was the task which I set myself.

At the beginning of all experimental work stands the choice of the appropriate technique of investigation. In many cases it has first to be created; it was so here as well. Although the method used to produce the results was of decisive importance, it can only be gone into in outline here. In the first place, satisfaction of two requirements was decisive, these two being a condition of the special circumstances in the central nervous system, which have been described: one concerns the technical devices, which were taken practically to the limits of refinement; the other is related to securing the minimum obstruction to the experimental animal's modes of expression. We would like to emphasize these two, because in these particulars American investigators, whose merit is beyond doubt (especially Ranson and Magoun), have followed another path, beset with various avoidable experimental errors. But, here as there, fundamental to the investigations lay the same principle which enables to obtain information, if one wishes to explore the layers and connections which lie below a surface: one applies "probes". In our case, artificial foci of excitation were produced with electrical impulses, and their effects noted. In addition, the technique of localized exclusion was also applied; as with disease foci, the reactions of this on the behaviour were interpreted in terms of disappearance of symptoms and were linked indirectly to the functional significance of the excluded substrata.

If I had thought, by observing the effects of artificial electrical stimuli in small doses on some dozen or so experimental animals with altogether some hundred points of stimulation distributed over the diencephalon, to achieve in due course the looked-for elucidation, then the first result was a thorough disappointment. The only positive finding which could be drawn from the first series, was the conclusion that the relationships obviously had a more complicated lay-out than had been thought, for the effects were so varied that no obedience to any law could be discovered. To meet this situation, the experiments had to be carried out on a considerably expanded basis. This was a simple enough conclusion; its realization was a different matter. It must be born in mind that one does not see directly - as is the case in the exploration of the surface of the brain - where the electrodes are attacking. Exact information about the functional significance of the deep sections of the brain is only obtained by working through the brain histologically in serial section. To avoid far too great delays, the experiments must be fitted in together as it were in time, and it is only possible to keep the material collected under control by using a carefully organized system of registration. The difficulty of finding one's way around in the abundance of individual observations was overcome by a graphic method. The extension of the experiments on the widest basis means time. To this is added the expenditure - for Swiss circumstances - of considerable funds. I make these last references on the one hand to make the slow growth of knowledge comprehensible, and on the other to be able to thank the various Swiss Foundations and above all the Rockefeller Foundation of New York for their financial support.

This short outline of the method of working brings us to the question of the results. As we go into these, certain motor effects, although they merit great interest, must be left on one side.

Now, concerning the influence of the diencephalon on the activity of the internal organs, the following facts could be disclosed: first of all, it has turned out that the functions which are mediated by the sympathetic section of the vegetative nervous system, are related to the posterior and middle parts of the deepest section of the hindbrain, i.e. of the hypothalamus. So the latter is to be considered, as it were, as the central area of origin of the sympathetic system. In order to give this discovery its full physiological import, some more elucidation is required. The goal of physiological research is functional nature. So in the course of this preoccupation with the vegetative nervous system, among other things the question has arisen of whether a circumscribed role is associated with the classical sympathetic system, which is defined primarily in terms of its area of origin, which is restricted to the thoracic spinal cord. An investigation undertaken from the viewpoint of the effect of its activity has yielded the finding that this is the case to a considerable extent. Where the sympathetic intervenes, it assists the body's efficiency and it aids the organism to greater success in its conflicts with its environment. It is functional, in so far as it behaves like an ergotropic or dynamogenic system. In addition to this item of knowledge there are still more findings which will interest the psychiatrist in particular, but also everyone who realizes that behind the variety of types of phenomenon stands the unity of the organism. On stimulation within a circumscribed area of the ergotropic (dynamogenic) zone, there regularly occurs namely a manifest change in mood. Even a formerly good-natured cat turns bad-tempered; it starts to spit and, when approached, launches a well-aimed attack. As the pupils simultaneously dilate widely and the hair bristles, a picture develops such as is shown by the cat if a dog attacks it while it cannot escape. The dilation of the pupils and the bristling hairs are easily comprehensible as a sympathetic effect; but the same cannot be made to hold good for the alteration in psychological behaviour. For this, only connections between hypothalamus, thalamus and cerebral cortex come into consideration. Functionally, the total behaviour of the animal illustrates the fact that, in the part of the diencephalon indicated, a meaningful association of physiological processes takes place, which is related on the one hand to the regulation of the internal organs, and on the other involves the functions directed outwards towards the environment. In other words: we know the key position in the diencephalon which has one aspect directed inwards and one aspect directed outwards. The sympathetic system is thereby, within the framework of a far-reaching organization, the mediating agent which intervenes particularly in the activity of the internal (vegetative) organs. With regard to the manifest influence of the psychomotor system and the psychological processes of association, a bridge is thrown over a gap, still wide open today, which lies between the purely somatically oriented physiology and psycho-physiology. It completes and broadens the insight into psychosomatic relationships, in the way they had been demonstrated by the great Russian physiologist Pavlov, who approached them from another side. To him also fell the great honour of speaking from this position.

In spite of the necessary restrictions on our exposition, observations of a different kind will induce us briefly to touch on the theme of somato-motor phenomena once again. Before this, another striking finding must be reported. The individual, vegetatively innervated, organ gets its differentiated innervation in the known peripheral organization of the sympathetic ergotropic system; correspondingly it can also be brought into action in isolation. This fact and the relationships, as they are met with, for example in the projection of the peripheral organs reacting to nervous stimulation in the motor area of the cerebral cortex, could give grounds for supposing that the individual internal organs also have a discrete representation in the diencephalon. In such an order of things the ergotropic zone would also be organized as it were by organs. The experimental findings offer proof that in reality the relationships are disposed differently. The fact is that even the most narrowly circumscribed forms of excitation and the most delicate stimulus dose never bring to light an isolated symptom related to one organ. In every case a group symptomatology makes its appearance. It is always groups of organs that are called into action, and indeed in such a way that the individual effects are combined, namely in accordance with the principle of synergistic coordination. Controls issue from the diencephalon which harness the functional capacities of individual organs in viable responses. This order of things holds good quite markedly in the ergotropic zone.

But under the influence of circumscribed stimuli applied to the hypothalamus, and partly also to the layers of the thalamus lying close above it, symptoms have also appeared which do not permit of classification in the sympathetic-ergotropic system of functions, and indeed rather act in opposition to this. The blood pressure, for example, does not respond by a rise, but by a fall; the heart rate does not increase, but rather decreases. At the same time respiration slows down, as opposed to the speeding-up which is obtained from the ergotropic-dynamogenic zone. Often a profuse flow of saliva occurs; further symptoms are choking and vomiting, micturition, defaecation. In other cases panting is caused, i.e. the mechanism most often seen in the dog under natural conditions, when it is hot. While the tongue, with its rich blood supply, moistened by a copious flow of saliva, hangs out of the wide-open mouth with the flow of air due to rapid respiration streaming over it, the discharge of excess heat takes place. This function, which is also common to the cat, serves the regulation of temperature and is in this sense equivalent to sweating (e.g. in man) when heat accumulates. Another effect of stimulation not mentioned so far is constriction of the pupils, followed by a drawing-across of the nictitating membrane.

To summarize, we are dealing with symptoms which are characteristic of a decrease in the influence due to the sympathetic system, and of an increase of parasympathetically transmitted excitation. Regarding the physiological effect, such reactions bring functional relaxation to the individual organs, or protection against overloading, but indeed protection above all. Where the digestive processes are concerned, the complex serving restoration is mediated by separate mechanisms. Since we give these related effects a common denominator in their functional aspect, the term "trophotropic system" is appropriate. Moreover the experimental findings show that a circumscribed region of the diencephalon corresponds to it, namely the anterior part of the hypothalamus, the area praeoptica, and the septum pellucidum as well. With this, a central, fairly clearly demonstrable division of the two partners of the vegetative nervous system becomes manifest. This is all the more noteworthy, as they are most intimately interwoven in their peripheral terminal territories. Important, too, is the establishment that there is no evidence in the trophotropic zone of a central organization corresponding to particular organs. It emerges conclusively from the effects obtained from the most varied sites of stimulation falling in the area named that here too no grouping is found in contrast, for example in the formation of nuclei; each particular syndrome shows a fairly large scatter. This does not, however, conceal the fact that some effects are preferentially released from certain larger areas. It is different in this respect from the ergotropiczone, where the group organization is more consistent.

We take a step forward, when we turn our attention to the observations from which it emerges that reciprocal mutual connections operate between the sympathetic-ergotropic and the parasympathetic-trophotropic areas, indeed in the sense that at each moment they produce a dynamic equilibrium adapted to the situation at any given moment of the organism as a whole. In this equilibrium the unity of the central regulation of the whole vegetative system is expressed. In the broad view, competition is a constructive principle

With this statement, we could conclude our exposition, that is, if we wanted to confine it to a more narrowly conceived theme. But among the fundamental results of the experimental exploration of the diencephalons alone was the finding that the effects produced from this part of the brain are not restricted to the vegetative system. Indeed the rule is that they are associated with somatomotor symptoms. When I refer to this, I do not have in mind the functions which testify to a higher order regulation of bodily posture within the framework of the extra-pyramidalmotor system. What we are discussing here concerns the motor symptomatology which stands in a specific relationship to the vegetative function. This is where our interest lies, if we attend briefly to this state of affairs. So let us look at a new stage in the integration of the organ functions in the total performance. In this way, for example, we can understand the experimental finding, that in many cases where the stimulus applied to the diencephalon causes defaecation, this is not brought about simply by peristalsis of the colon and rectum. In particular, where a stimulus is applied to the most rostrally situated regions, the cat adopts the normal posture for the physiological deposition of faeces; therefore the stimulus activates the skeletal musculature, which is innervated by the cerebrospinal axis, and which is also responsible for the abdominal muscular pressure. It was possible to make the same observation during micturition. The synergistic coordination between the function released through the vegetative nervous system and the somatomotor complement is manifest. An improvement in the result is obtained, partly in the form of a speeding-up of the process, and partly in the way soiling is avoided.

Particularly impressive is the synergistic coordination of mechanisms controlled by the vegetative nervous system with cerebrospinal innervated activities in the defence mechanism which is accompanied by emotion. This had already been the subject of discussion, but without any particular light being thrown on the structure of the action as a whole in relation to the systematic involvement of somatomotor phenomena. Dilation of the pupils, bristling of the hair are the vegetative components, and snuffling and spitting as somatomotor processes complete the picture intended to scare off the opponent. The aimed blow with the paw conclusively presupposes a visual orientation, which, while compulsive in affect, nevertheless fits in adaptively because of the intervention of the cortex. Thus one sees how the various levels make their contribution to the full success of a complete activity, and one understands how individual functions are associated in stages in an activity carried out by the organism as a whole.

According to this view of how the diencephalon plays a decisive role in activity which progresses from the part to the whole, it will come as no surprise if still other observations could be made which lead in another direction. Thus it has been seen that under defined experimental conditions a constriction of the pupil and a drawing-across of the nictitating membrane may be caused from a certain region of the diencephalon. A slowly developing narrowing of the palpebral fissure accompanies these events, which reflect a decrease in the sympathetic innervation, which - particularly in the pupil - occurs with an increase in parasympathetic influence. These effects also are not infrequently associated with certain symptoms under the nervous control of the central nervous system: the drooping of the upper eyelid develops into an active closing of the lid. Simultaneously the head droops, whereupon, as the syndrome develops further, the whole animal lies down. It is necessary to observe this process accurately in its development and in the final stage; it will be noticed, as you will realize, that the cat does not simply collapse, as is the case with generalized loss of tone. Under the influence of gradual relaxation the animal choses its place and curls up. Altogether a picture results like that known under physiological conditions only in the sleeping cat. In a certain sense one is presented with the mirror-image of the emotionally aroused cat with increased excitability; for the readiness to react to sensory stimuli is markedly decreased, whereby - as in the normal sleeping cat - the tickle reflex of the ear stays "awake". Behaviour towards olfactory stimuli is also relatively little inhibited, which are effective as a more potent arousal stimulus, thereby proving the reversibility of the whole process. In other respects, as has been mentioned, the preparedness for energetic activity is reduced to a minimum. Clearly, in the competition between ergotropic and trophotropic systems the former forfeits some of its influence on the organism as a whole in favour of an excess of the latter. But it must always be borne in mind that we are dealing with the result of artificial stimulation, and indeed in a limited area. To explain the gradual development of this inhibition of activity as the result of destruction in the hypothalamus is misleading. On the other hand it is correct that one is dealing with a protective function controlled from the diencephalon, which avoids exhaustion and produces the conditions for an undisturbed recovery. The latter - judging by the physiological sleep - particularly concerns the higher centres. For the rest, as regards the where and the why, electroenceph-alography, e.g. in the line of research by Jasper, and biochemistry have the say in the matter now. So the investigations, which have been reported here, have, as is the rule, in addition to a clear understanding also brought into focus the formulation of new questions.

Now that we have come full cycle with the investigation in which the integrating activity of the diencephalon was experimentally differentiated, I would very much like to show some more pictures, with which the spoken word will be clarified. The time available, of course, permits only a limited selection of slides and a film. But I think they are enough to provide an objective representation of what has been said.

1. The following were shown, as *lantern slides*: rise in blood pressure, fall in blood pressure, increase of respiration, slowing of respiration; in the *film*: methodology - dilation of pupils, retraction of the nictitating membrane, defaecation, retching, panting - licking movements, chewing movements, sniffing movements - affective reactions: spitting, bristling of hair, leaping to attack, urge to eat, urge to flee - atonia as an effect of stimulation - adynamia as an effect of exclusion - sleep as the effect of stimulation.
2. The following localizing findings were presented: medium section of the cat's brain and further sagittal sections with symbols marked in (lowering blood pressure, raising blood pressure, pupil dilation, pupil constriction, affective defence, hunger drive).

From *Nobel Lectures, Physiology or Medicine 1942-1962*, Elsevier Publishing Company, Amsterdam, 1964

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