ON THE RESPECTIVE PARTS PLAYED BY NEURAL AND HUMORAL INFLUENCES IN ANIMAL REACTIONS.

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Until comparatively recent years it was held that all reactions in those Metazoa in which a nervous system has become evolved are produced by the effect of a sensory stimulus transmitted by a nerve-fibre to a nerve-centre and reflected or relayed to an efferent fibre, which in its turn causes a stimulus to set going the effector agent—muscle-fibre, gland-cell, pigment-cell, etc. In the most lowly organized Metazoa in which no nervous system has been discovered, and in plants in which nothing similar to the nervous system of animals exists, there may occur a transmission of the effect of a sensory stimulus from cell to cell, whether by contiguity or continuity of protoplasm, and this may set up actual movements in a distant part of the organism. Such movements are apparently caused by alterations in turgor, and are very similar both in their obvious effects and in the accompanying phenomena (electrical changes, etc.) to the effects produced by reflex stimulation in higher animal organisms. The transmission from cell to cell may be termed "pseudo-neural," for the effect is the same as if a nervous system existed, although it occurs more slowly. Indeed some observers, relying upon the results of external stimuli, have assumed the existence of a nervous system in plants as well as in animals. There is, however, no anatomical basis for such an assumption.

Some 30 or more years ago it was discovered that special chemical substances are formed in certain organs—which substances when passed into the blood influence other structures of the body and excite them to activity, causing distant effects (contraction, secretion, etc.)—which had previously only been known to be produced under the influence of the nervous system. This discovery furnished

evidence of the probability that the functions of the organs are not only under neural control, but are also subject to chemical control, by means of active materials which reach them through the blood. Such chemical influences are distinguished as "humoral" from the "neural" and "pseudo-neural" influences above mentioned.

Although in the modern sense the idea of chemical governance is new, the term humoral was formerly used in medicine to express the notion that the health of the body is affected by the condition of and alterations in the humours of the body, chief of which was considered to be the blood.

The first discovered of these special chemical substances was obtained from the adrenals; it is still the best known. It influences plain muscle, secreting cells, pigment-cells, and speaking generally all structures which are supplied by sympathetic nerve-fibres. It is produced by cells which are morphologically equivalent to the nerve-cells which give rise to sympathetic nerve-fibres. They have the same origin, but instead of developing into elements of the nervous system and giving off nerve-fibres to influence distant parts, the cells remain without processes and develop into the secreting cells of the medulla of the adrenals, producing the special chemical substance *adrenaline* (epinephrine), which is passed directly into the blood. By this fluid it is carried to other parts and influences the organs in the same manner as they are influenced by the sympathetic nerves by which they are supplied. Whether the tissues are acted upon in such a way that their activity is increased (excitation) or diminished (inhibition), the result is the same for both neural and humoral influences, *e.g.* the muscular tissue of the bloodvessels which is caused to contract by stimulation of sympathetic nerves, is contracted by adrenaline, and the muscular tissue of the intestines, which is prevented from contracting (or inhibited) by stimulation of sympathetic nerves is also inhibited by adrenaline.

Another chemical substance of this kind is secretin—which was appropriately termed a "chemical messenger" by its discoverers, Bayliss and Starling. This is formed in the intestinal mucous membrane and taken up by the blood. It influences the secretion of pancreatic juice, causing it to be poured out in abundance. So far as is known secretin has a purely excitatory effect, a character which was accentuated by Starling by its inclusion in a class of chemical

substances which have the property of exciting organs to activity when introduced into the blood; all such substances he termed hormones (ὁρμάω, I excite), and included in the group even such a simple chemical substance as CO_2, which is produced in the tissues, passed into the blood, and excites the respiratory centre to activity.

Starling's term "hormone" has been diverted from the sense in which he originally employed it, and is used by other physiologists to include chemical substances which, so far from exciting tissues to activity, have exactly the opposite effect, that, namely, of restraining or preventing their activity. For, just as we have nerve-fibres which excite or increase the activity of an organ and nerve-fibres which stop or diminish their activity, so we have chemical agents formed within cells and passed into the blood some of which excite other cells to activity, and others, so far from exciting, restrain or prevent their activity. Their effect is, therefore, in no sense hormonic or excitatory, but on the contrary, is restraining or inhibitory. In either case it is humoral, that is, it acts through the blood.

The action of these chemical agents, whether they excite or restrain, is similar to that of drugs, with which they will bear close comparison. Indeed, several such substances are used in medicine as drugs. On this account the term "autacoid" (αὐτός, self; ἄκος, a remedy) which includes both kinds, has been suggested for them, as more correct for general use than "hormone" which implies one kind of action only. An autacoid which excites a tissue to activity is a hormone; one which prevents or restrains activity is termed in contradistinction a "chalone" (χαλάω, I restrain). Some autacoids are purely hormonic or purely chalonic: others may act in the one or the other way according to the nature and conditions of the tissue acted upon: in other words they are neither pure hormones nor pure chalones.

This much having been stated as an introduction to the terminology of the subject we may proceed to consider what part is played respectively by nerves and by autacoid substances in the regulation of physiological functions.

In the first place it may be remarked that, so far as is known, every tissue and organ of the body of the higher animals is under *neural* control, while, with regard to certain tissues and organs, it has not yet been shown that they are also under *humoral* control. Of the latter the voluntary muscles and the salivary glands furnish

the best known examples. It is further to be noted that in all cases in which the double control exists the neural action is the more rapid, the humoral action coming on later and being more prolonged. Sometimes the same nerve[1] carries both the impulses which directly cause increased activity of a tissue and those which provoke the secretion of an autacoid; this autacoid then carries on the action, originally purely neural, by furnishing a chemical stimulus to the tissue. One of the best known instances is furnished by the effects produced on the organs of the vascular system by reflex stimulation; these effects, started by direct neural action, are carried on by autacoidal action, the secretion of the autacoid being evoked by the same stimulation.

In every case the neural control appears to be the primary effect, the humoral the secondary. Nevertheless, there may be humoral control without apparent direct nervous control. This seems to be the case with the mammary gland, in which no direct neural influence has hitherto been shown to occur, although the humoral effects are well marked (action of corpus luteum extract and of pituitary extract). In the kidney also no direct neural influence upon the secretion has been shown to occur, although there is some proof of humoral influence.

Of late years there has been evidence brought forward, although as yet hardly as conclusive as might be desired, that the excitation of a nerve-fibre may produce within the tissue which it influences a chemical substance or autacoid which acts directly upon the tissue, and tends to prolong the action which has been started by excitation of the nerve. It has been known since the action of the vagus upon the heart was discovered that the inhibitory effect does not cease at the moment the excitation of the nerve is arrested, but is prolonged for an appreciable time afterwards. The cause of this prolongation of effect was not understood, but it has been affirmed by many investigators that an extract of cardiac tissue which has been inhibited for a short time by vagal excitation will, if perfused through another heart, cause it to beat more slowly: in other words, that an inhibitory autacoid (chalone) has been produced within the tissue and continues the action caused by the nerve. On the other hand stimulation of the sympathetic nerve-fibres will directly cause cardiac acceleration, and this effect also is prolonged for an appreciable time after the stimulation has ceased. The prolongation has been similarly referred to the formation of an exciting

[1] This statement does not imply that the impulses are carried by the same nerve-fibres, which is certainly always not the case.

autacoid (hormone) in the tissue itself, which serves to continue the excitatory effect of the nerve-fibres.

These instances of humoral action are somewhat different from those which have been longer known, for the chemical agent or autacoid is assumed to be produced within the tissue upon which it acts. It may even be that in such cases the effect of the nerve-impulses is itself produced through a chemical agent, the nerve-impulses themselves merely causing the production of the specific autacoid, and this producing the effects (inhibition or acceleration) observed. In the case of the cardiac nerves the long latency period which elapses between the commencement of the nerve-stimulation and its effect seems to favour this hypothesis.

Although it might be contended that a humoral (chemical) control, independent of nervous action, is a simpler form of activity requiring no elaborate apparatus for its distribution, and on that account might be assumed to be a primary form of regulation of function evolved before the development of a nervous system, nevertheless, as we have seen, the evidence of experiment points to the neural action being primary, the humoral secondary. And if we turn to the evidence afforded by evolution the probability becomes accentuated that autacoidal or humoral control must be regarded as a secondary effect and neural as primary. For the lowest Metazoa in which a nervous system has been detected, *viz.* the Cœlenterata, possess no circulatory fluid which could convey chemical agents to distant parts of the organism. Moreover, such fluid as bathes their tissues does not differ materially from that of the medium in which they exist. But their nervous system is constructed of elements similar to the nerve-cells and -fibres of higher animals, the nerve-units (neurones) being completely separate, and any propagation from one to the other, or from nerve to muscle being effected by contiguity and not by continuity. In the common medusa of our seas the muscular layer of the sub-umbrella is covered with a close plexus —not a network[2]—of simple or simply branched nerve-cells, bipolar

[2] The nerve-plexus is often spoken of as a nerve-network, but the cell-processes do not unite with one another to form a network: the cells always remain distinct and separate units, as in the case of the nervous system of vertebrates. For evidence of this see Schäfer, E. A., Observations on the nervous system of *Aurelia aurita*, *Phil. Tr.*, 1878, clxix, pt. ii, 563. This paper appeared long before the formulation of the neurone doctrine and at a time when it was universally held that the elements of the nervous system were in all cases united to form a network.

in form, each pole being prolonged into a nerve-fibre, which in no instance joins another nerve-fibre, although coming in frequent contact with other fibres. In this way the excitation which is sent out by nerve-centres at the margin of the disc is transmitted to the whole of the muscular sheet and a coordinated movement of the umbrella is produced.

The above considerations, derived equally from the results of experiment and from the study of evolution, render it probable that neural influences play the primary part in inhibiting and controlling animal reactions, and that the part played by humoral influences, although in many cases a useful and even a necessary auxiliary, is, nevertheless, secondary to that played by the nervous system.

It is obviously of physiological importance that reactions such as that of movement away from or towards a source of stimulus, according as it is hurtful or useful to the organism, should be as rapid as possible, whereas the production and action of a chemical stimulus must necessarily be slower. On the other hand prolongation of the neural effect by the action of a chemical agent would serve to economise nervous energy.

CONCLUSIONS.

1. In the higher animals control of the functions of the body is dual, being partly neural and partly humoral.

2. When the control of any function is single and not dual, it is entirely neural. Exceptions to this statement appear to occur in connexion with the secretion of urine and milk, since these functions have not hitherto been shown to be under direct neural control. The mamma, and perhaps the kidney also, is, however, influenced by certain internal secretions which are themselves subject both to neural and to humoral control.

3. The functions which are controlled both neurally and humorally are initiated by direct nervous influence: the humoral influence succeeds this.

4. In the lowest organisms possessed of a nervous system there is no evidence of humoral control, and no probability that this could be exercised, since there is no circulatory fluid, and the fluid which

bathes the tissue has a composition appreciably the same as that of the environment.

5. It is, therefore, inferred that in all cases in which a dual control exists the neural, which is more rapid in its action, is primary, and the humoral secondary; and that the object of the humoral influence is to continue and prolong the effect of the neural influence, and thus to effect an economy of nervous energy.