THE REGULATING AND REFLEX PROCESS.*

BY

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PART IV.—NERVE CENTRES: THEIR CONSTITUTION AND SIGNIFICANCE.

THE term "nerve centre" is applied to a collection of nerve cells in the central nervous system which are associated together in the performance of some particular function. The term is a very elastic one and is used to denote a number of different conceptions. Its very elasticity makes its use convenient, but the term lacks precision and is apt to obscure the conditions which really exist. The nerve cell is only a part of the neurone, and its axis cylinder, its more important element in conducting the nerve impulse, may extend to great distances from the cell body. The term ascribes to the cell body of the neurone an importance which the facts do not warrant.

A collection of nerve cells—the cytons or cell bodies of the neurones, which give origin to an efferent nerve—is known anatomically as the nucleus of the nerve. It may also be termed an efferent nerve centre, and the neurones of which it is composed carry nerve impulses from the central nervous system to the rest of the body. The anatomical nucleus of the afferent nerve presents an important difference. It also lies in the central nervous system, but its cytons do not give origin to the peripheral afferent neurones, and are always separated from the latter by synapses. The cells of origin of the afferent neurones are found in the ganglia of the posterior nerve roots of the spinal cord and in the corresponding cranial ganglia. The impulses they receive at the periphery are carried into synapses before they reach the neurones of the afferent centre, and are therefore liable to all those influences which the synapse is capable of exercising.

The efferent neurones not only innervate certain structures in the periphery but also exert some kind of nutritive influence over them. If they supply voluntary muscle, that muscle fails to develop properly if the efferent neurone does not also develop, and injury to the neurone or centre leads to secondary changes in the muscle of a retrogressive nature. The afferent centre, on the other hand, is separated from the peripheral afferent neurone by an irreciprocal synapse, and is therefore unable to exercise any control over the peripheral neurone. Injury to the afferent centre may leave the peripheral neurone intact and able to maintain the nutritive functions it possesses by its axon reflexes.

Anatomically, therefore, there may be an afferent or receiving centre and an efferent or distributing centre in a reflex arc. But the reflex does not necessarily require either of them, the axon reflex being an example. In other cases there may be no afferent centre. There is evidence that in a deep tendon reflex, such as the knee-jerk, the afferent nerve impulse is conveyed directly to the peripheral efferent neurone, and there is only one synapse in the reflex arc. In the majority of reflex arcs more than two neurones are concerned, and consequently there is more than one synapse in the chain. An example of a nerve centre in which there are many neurones concerned is furnished by the cerebellum. The cerebellum is essentially an afferent centre which receives nerve impulses from proprioceptors in the body. The nerve impulses have passed through at least one synapse before reaching the cerebellum, a fact of very great importance, because opportunity is thereby afforded for the spread of the impulse to other pathways, with the resulting production of pain and other phenomena. The afferent centre in the cerebellum is in turn able to excite

efferent neurones, the cells of Purkinje, which distribute the impulses to efferent neurones in other parts of the nervous system. The reflex through the cerebellar arc is therefore an example of one in which there are a number of neurones and synapses concerned. Reflexes through the cerebrum appear to be carried over even more complex arcs, and the possibilities of spread of the nerve impulse, and of its inhibition or diversion into other pathways, is correspondingly greater.

CONSTITUTION OF NERVE CENTRES.

Physiologists employ the term "nerve centre" to denote collections of nerve cells in the central nervous system which are associated with the co-ordination of some definite physiological function. The anatomical units of which they are constituted are not always definitely located, and in some cases the centres are assumed to be present in certain positions although their very existence may be hypothetical. The heat-regulating centre is said to exist in the corpus striatum, and to control the nervous processes which regulate the production and loss of heat by the body. The centre is supposed to be directly influenced by the temperature of the blood in the blood vessels in its vicinity. If such action does occur it is unlikely that the body of the nerve cell in the centre is the site of stimulation by the change of temperature. It is possible that there are in it special receptors which are stimulated by changes in temperature, but far more likely that the synapses are the parts affected. To say that the centre is controlled by the temperature of the blood circulating through it is no explanation of where and how the action takes place. Variations in the resistances of the synapses in the centre as the result of changes in temperature afford a working explanation.

The same ambiguity attaches itself to other centres which are supposed to be the sites of a direct action by outside agencies. The respiratory centre is in some way influenced by the concentration of the hydrogen ion in its vicinity. The part stimulated by the hydrogen ion may be, as implied by Haldane, special receptors in the dendrons of cells in the centre, but it appears to us to be more likely that the hydrogen ion affects the resistance of the synapses in such a way that the afferent impulses are differently distributed and thus lead to alterations in the nerve impulses which leave the centre along the efferent neurones. The respiratory centre is generally considered to possess the power of automatism and to be the site of rhythmical discharges of nerve impulses. This automatism, if ever present, disappears during the condition of apnoea induced by the artificial diminution of the hydrogen ion concentration of the blood. It is never stated in what part of the respiratory centre the power of automatism resides. When one attempts to analyse the respiratory centre many difficulties are met with. The centre has been roughly located by physiological experiments in an area in the medulla oblongata in the neighbourhood of the afferent nucleus of the vagus nerve. Afferent nerve impulses are carried to it by the pulmonary branches of the vagus and give rise to the Hering-Breuer reflex. Afferent nerve impulses are also carried to it from numerous other sources, but whether they all go to the afferent nucleus of the vagus or to other neurones on the efferent side is unknown. The position, too, of the special receptors, if such exist, is not known. The synapses on the afferent side of the centre must be capable of alternation between excitation and inhibition, and of varying degrees of resistance to the passage of nerve impulses.

Provision is made for reciprocal innervation. The afferent impulses, whether from the pulmonary fibres of the vagus or from the afferent fibres of the nerves supplying the muscles of respiration, must inhibit certain neurones and excite others so as to bring about a proper co-ordination of the efferent nerve impulses to the muscles of inspiration and expiration respectively. The terminal efferent neurones leave the central nervous system at various levels according to the muscles they supply, and their cells of origin are found at considerable distances from the actual centre. The centre is also similarly controlled by nerve

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impulses from the higher levels. The incoming nerve impulse may cause inhibition of expiration and excitation of inspiration or the reverse. In the case of some afferent impulses their action may be directed solely to the production of inspiration or expiration. The application of cold to the skin brings about inspiration, while stimulation of the mucous membrane of the larynx excites a violent expiration with the other movements associated with coughing.

The passage of the nerve impulses through the centre may be varied in a number of ways. They may be directed into the efferent inspiratory and expiratory neurones alternately for different periods of time. If alternating rapidly the movements of respiration are quick. If alternating slowly the respirations are slow. The depth of the respirations probably depends upon the number of neurones concerned as well as upon the rhythm. It is possible that we have constant variations going on in the neurones affected during quiet respiration, first one set and then another coming into action, fluctuation taking place just as it has been shown to occur in the capillary circulation. When the stimulus to respiration is powerful the impulses spread very widely over the efferent neurones, but alternate between inspiration and expiration. The number of neurones concerned in respiration is very variable. Even in quiet respiration the neurones affected are spread over a wide area, but in dyspnoea practically all parts of the lower level of the central nervous system are concerned on the efferent side. The nerve impulses seem, however, to come from the centre in the medulla oblongata and to be distributed from it to the efferent neurones.

If automatism is claimed for the centre it is difficult to see where this property is to be located. It cannot be in the efferent neurones, for the centre of the phrenic nerve shows no sign of it when isolated. If in the afferent nucleus of the vagus nerve, it is difficult to see how respiration is made to alternate between inspiration and expiration and is at the same time subject to control by other incoming nerve impulses. It is much simpler to regard the neurones as having the same property as other neurones elsewhere, and as responding only to nerve impulses coming to them from other neurones. The centre is affected in disease. Its activity is increased in febrile conditions, and Haldane has shown that fatigue of the centre results in rapid shallow breathing. It is unlikely that fatigue or the toxins of disease act primarily upon the cell bodies of the neurones; they are far more likely to bring about their results by action upon the synapses on the nerve pathways in the centre. In the rapid shallow breathing of fatigue the blood may be imperfectly aerated, yet the stimulus of the hydrogen ion content is ineffective and does not bring about a sufficient depth of respiratory movement to ventilate the lungs. The special receptor, if it exists, might be the site of the fatigue, but fatigue of the centre may be caused by breathing against a resistance, and in such case there is nothing to fatigue the special receptors. The evidence seems clearly to be in favour of a synapse fatigue.

More is probably known about the respiratory centre than about any of the others, but our knowledge of it is far from satisfactory. The vasomotor centre is another of the vital centres which presents similar problems. Unlike the respiratory centre it is unaffected by voluntary influence but is subject to changes by the nerve impulses underlying emotional states. It is also supposed to be directly influenced by conditions of the blood. Here again such influence is better explained by changes in resistance of the synapses than by the postulation of special receptors in the centre.

Drugs are often stated to exert their influence by direct action upon certain centres. Apomorphine is said to stimulate the vomiting centre. If it does have a direct action upon the centre the site of its action is most probably upon the synapses and not upon the neurones or special receptors.

If we are to regard the neurone as a conducting mechanism and not as an automatic generator of nerve impulses, the nerve centre may be looked upon as a net-

work of nerve pathways which are so arranged as to conduct the nerve impulses in definite channels for the sake of obtaining a co-ordinated end-result. Certain pathways are, as it were, canalized in the centre, and incoming nerve impulses are directed and distributed to the efferent neurones. The controlling influence in the nerve centre is not the nerve cell but the synapses. We prefer to define the nerve centre as a collection of nerve pathways or neurones which are so arranged that nerve impulses coming into them are co-ordinated and distributed to bring about a definite end-result. The co-ordination and distribution effected in the centre depend upon changes in the synapses. The synapse is the all-important factor in the centre, and is the probable site of the action of fatigue and of other extraneous influences.

FORMATION OF PATHWAYS OR CENTRES.

Some pathways or centres are preformed in the embryo. Their anatomical arrangement is such that afferent impulses coming into them bring about a definite end-result which is not the product of education. The vital reflexes of the body are examples. Most of these, such as the respiratory, cardiac, and vasomotor reflexes, remain during the whole of life. The sucking reflex of the newly born child is an example of one in which the centre is preformed but does not persist. Other centres are educated, and we have seen that the process of education consists largely in the cultivation of the synapses so that nerve impulses pass readily over some and not over others.

An interesting and important development of the postural reflexes takes place after birth in the child, and the pathways of the nerve impulses concerned are slowly educated. The attitude of the child, or its postural position *in utero*, is one of flexion. In the newly born child the muscles which produce flexion at a joint are more developed than are the opposing muscles. After birth an erect posture, or one of extension, is gradually assumed, and a long time elapses before the extensor muscles attain the relatively greater strength which characterizes them in the adult. With the development of new reflex paths the extensor muscles gradually assume a predominance. Failure to develop the new postural reflexes is a matter of considerable clinical importance, and, according to Blundell Bankart, is the real cause of the deformities which so commonly appear in the lower extremities and spine. Talipes, lateral curvature, and other deformities are explainable by the failure of the nervous system to lay down the particular pathways or centres which are requisite for the proper development of the muscles.

The response of the plantar reflex in the child differs from that in later life, and the explanation is probably to be found in the difference in development of the nerve pathways for the flexor and extensor muscles at the ankle-joint.

In the case of all reflexes which are in constant action there must be some provision against fatigue. This is probably effected by there being a sufficient number of pathways in the centre to allow of fluctuation. We may assume that the units in action are constantly changing within certain limits. When all are called into action simultaneously greater effects are produced and fatigue is more readily caused. An increase in the number of pathways concerned in a reflex may lead to greater spread in the central nervous system, but it is probable that some other factor is necessary such as the increased frequency of the impulses carried. The increased frequency may be the main factor in overcoming the resistance of other synapses and so causing spread beyond the usual channels. We know that the impulses do spread widely under certain conditions, and the spreading may be the result of a massive action of afferent impulses, or of a lessened resistance of the synapses as is induced by the action of strychnine.

Reflex pathways or centres which are preformed and persistent are concerned in the production of the unconditioned reflex. Such reflexes take place with a considerable degree of certainty although they are not altogether independent,

and can be more or less influenced by nerve impulses from higher levels, especially by those which are concerned in emotional states.

Other centres, or pathways, are formed by education, and this is particularly the case in those reflexes which take place through the cerebral cortex. Such reflexes are "conditioned," and are therefore liable to various alterations and especially to inhibition.

Functional centres or pathways may be formed in abnormal states. Fixed ideas probably result from the establishment of certain pathways in the cortex of the cerebrum. In asthma afferent nerve impulses resulting from certain stimuli produce a reflex contraction of the bronchial muscle and a narrowing of the bronchioles. The reflex may become a "conditioned" one, and be induced by any afferent impulse resulting from a stimulus which has been associated with its occurrence. The pathways in time are so "grooved" that the reflex takes place very readily, and is excited by any afferent nerve impulse which has previously been associated with the asthma.

The phenomenon of pain, and especially of visceral pain, may be influenced in the same way. The frequent carriage of nerve impulses from the heart along the pain paths results in a lessened resistance of the synapses along the pathways taken. The occurrence of pain is facilitated, and a condition of status anginosus may be set up in which afferent impulses from other sources may spread into the same paths and produce pain. An attack of angina may be induced in this condition by a carious tooth or other source of pain.

In the production of visceral pain the afferent impulses from the organ affected spread into the pain paths in the lower level of the central nervous system, but the sensation of pain is located in some part of the body wall which is supplied with afferent nerves the impulses in which are capable of exciting a more or less localized sensation. In the areas supplied by these nerves various phenomena occur. Hyperaesthesia is sometimes met with, and the margins of the hyperaesthetic area are constantly varying in position. The hyperaesthesia is probably due to a decreased resistance of the synapses leading to the pain pathways, so that nerve impulses which would not ordinarily cause pain now do so because they pass more readily into the pain pathways.

The fluctuation in the extent of the area affected may be due to variations in resistance of the synapses in the pathways of the afferent neurones coming from the borders of the area, and be ascribable to the phenomenon of fluctuation or variation in the actual units employed in carrying the nerve impulses.

But other changes than sensory are usually found. Increased tone, or the actual contraction of muscle, often occurs in the body wall. The rigidity of muscle, especially well seen in the abdominal wall as the result of irritation of an abdominal viscus, is a reflex phenomenon, and is subject to the same variations as that affecting the sensory changes. A temporary centre is created in the central nervous system, and afferent impulses from the irritated viscus make use of certain pathways with the production of a number of end-results. If the afferent impulses are sufficiently numerous, or if there is any condition present which decreases the resistance of the synapses, the impulses may spread and occasion not only pain, hyperaesthesia, and contraction of muscle in a definite area, but vomiting, cardiac, vasomotor, and other reflexes.

Sensation and reflex action are closely bound up together. Even visceral reflexes may be productive of sensation. Alterations in the heart beat, palpitation, respiratory disturbances, vaso-constriction, and vaso-dilatation give rise to subjective phenomena. Irritability, exhaustion, and depression are of common occurrence in ill health. The fatigue of a synapse renders that synapse more resistant to the passage of a nerve impulse, and fatigue of the afferent pathways should be a negation. But fatigue and the sensations met with in ill health are positive sensations and not mere negations. They are, as a rule, general and not localized to any particular part. Their cause is unknown, but must be sought for in some alteration in the afferent nerve impulses affecting the conscious state.

REPORT OF THREE AUTOPSIES FOLLOWING CARBON TETRACHLORIDE TREATMENT.

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WITH the object of confirming the report that carbon tetrachloride may produce pathological lesions of the liver,* a number of condemned prisoners were treated with small doses of the drug. *Post-mortem* examinations were made on three of the prisoners. In two cases the intestines were removed in three sections after double ligatures had been applied; the sections were opened and washed separately to determine the number of free and attached parasites in each.

Each prisoner received 4 c.cm. of carbon tetrachloride, followed in two hours by 2 oz. of saturated Epsom salt solution. No food was allowed previous to treatment except in the case of No. 8925, who by mistake received his ordinary breakfast at 6 a.m., and was treated at 10 instead of 8 in order to permit the passage of the food into the intestines. One and a half hours after the administration of the salts they were allowed tiffin.

Prisoner 8925 received 4 c.cm. carbon tetrachloride at 10 a.m. on February 21st, the salts at noon, and had tiffin at 1.30 p.m. The number of worms counted in the first twenty-four hours was: hookworms 101 (male 38, female 63), ascaris 1, oxyuris over 1,000. In the second and third periods of twenty-four hours no worms were found. The man was executed on February 24th. In the contents of the large intestine two oxyuris and two trichuris were found, and attached to its walls nine trichuris and twelve oxyuris. In the lower two-thirds of the small intestine three ascaris were found in the contents and one ascaris and one trichuris attached. Two ascaris were attached to the duodenum and upper third of the small intestine. Prisoner 8937 received 4 c.cm. carbon tetrachloride at 8 a.m., the salts at 10 a.m., and had tiffin at 11.30. During the first twenty-four hours one hookworm (female) was found and one oxyuris. In the second and third periods of twenty-four hours no worms were found; he was executed on February 24th at 8 a.m. In the contents of the large intestine eight hookworms (six male and two female) were found and two trichuris. Three other trichuris were attached to the walls. In the contents of the lower two-thirds of the small intestine one ascaris was found, and two trichuris attached to the wall; no worms were found in the duodenum and upper third of the small intestine. Another prisoner 8992, received 4 c.cm. of carbon tetrachloride, but in his case the worms were not counted, nor were the intestines examined. None of the patients made any complaint.

Sections of the organs were stained with osmic acid according to the method of Marchi. Sections also were stained by haemotoxin and eosin.

No. 8925.—The liver showed fatty degeneration, many of the cells containing fat globules; the largest of the globules measured about 10 microns. The kidney cells contained a few globules of fat. The spleen was greatly enlarged and showed pigment and fibrotic changes due to numerous attacks of malaria.

No. 8937.—The liver showed slight fatty degeneration, the kidney no recognizable changes.

No. 8992 showed no changes in liver or kidney.

Conclusions.

1. A dose of 4 c.cm. of carbon tetrachloride given as in the above cases may produce fatty degeneration of the liver.

2. Although numerous fat globules may appear in the liver cells apparently as a result of the administration of carbon tetrachloride, the changes in the liver are of a temporary nature and do not appear to contraindicate the use of the drug, because many patients have been treated with much larger doses and have not complained of any discomfort other than very slight giddiness, nor have symptoms or signs of ill health arisen in them. Further, many hundreds of school children have received doses of carbon tetrachloride, and in no case has any sign of ill health occurred subsequent to treatment.

3. In case No. 8925 the changes in the liver were so marked that we would have expected signs of marked ill health during life, but these were absent; consequently it appears that much fat (presumably derived from fatty degeneration) may appear in the liver and yet be a matter of small importance as concerns the health of the patient.

* Docherty, J. F., and Burgess, E.: Action of Carbon Tetrachloride on the Liver, BRITISH MEDICAL JOURNAL, November 11th, 1922, p. 907.