A Preliminary Inquiry

INTO

THE NATURE OF THE CELL IMPULSE.

BY

SIR JAMES MACKENZIE, M.D., F.R.C.P., F.R.S.

(From the St. Andrews Clinical Institute.)

STIMULATION.

THE process of stimulation is recognized as the response of the cell to an impulse. This process forms the basis of all vital activity. It is recognized that the organs of the body are constantly assailed by impulses from without or from within the body, the impulses being generated by the functional activity of the organs.

While this description indicates the nature of stimulation, there is still much that is obscure about the manner in which it is carried on in the maintenance of life. When, for instance, the physiologist applies an electric stimulation to the cut end of a sympathetic nerve, and produces an increase in the contraction of the heart, the experiment is spoken of as a stimulation of the heart. But this is an end-result, and the physiologist cannot explain what took place between the cut nerve and the muscle contraction. Many symptoms of disease are the results of increased activity of organs which are said to be stimulated, but here again the symptom is but an end-result, and it is not known how it was brought about.

In our investigations into symptoms it was manifest that little progress would be made until we had an understanding of the processes which led up to the end-result. In our search for this fuller knowledge we had occasion to investigate the functions of the conducting system of the heart. It may be pointed out that until the part played by the conducting system in the heart beat is understood it will be impossible to interpret fully and correctly any action of the heart, experimental or clinical.

When we considered the pulse beat which occurred in auricular fibrillation and flutter we came across a condition which threw some light upon stimulation. It is now recognized that the contraction of the ventricle is dependent upon the auriculo-ventricular node, and we can infer the condition of the node by the character of the radial pulse. The advantage of studying this node in these conditions lies in the fact that the impulses which stimulate the node are constant in number. In auricular fibrillation they are innumerable; in auricular flutter they are within the neighbourhood of 300 per minute. When the body is at rest the pulse rate may have fallen to 50 or 40 beats per minute. When moderate effort is made the pulse rate may rise to 140 or 150 beats per minute. As the impulses are constant in number, this variation in rate can only be due to a variation in the excitability of the cells of the auriculo-ventricular node. This is an illustration of stimulation arising through an increased excitability of cells. How that comes about has been an object of study, but it does not immediately concern the purpose of this paper.

Having considered the excitability of the cell, we turned next to consider the other factor—namely, the impulse. It is well known that the heart muscle cells, when they contract, throw out impulses. The questions arose, Was this function peculiar to the heart muscle cells? or was it common to all muscle cells? The answer to this latter question was easily given in the affirmative. We had but to consider what happened in a uterine contraction to recognize that large numbers of impulses were generated. These impulses are taken up and conveyed by afferent nerves into the central nervous system, and give rise to a series of reactions in remote organs, such as increased pulse rate, flushing, sweating, pain, nausea, and vomiting. Here, then, was another form of stimulation due to the increased number of impulses.

The Impulse.

As our inquiry proceeded we found that the interplay between impulse and cell excitability was regulated and controlled by certain very definite laws, and it was by the

operation of these laws that the activity of organs was modified to meet the requirements of daily life. But to understand these laws we require a fuller knowledge of the impulse. It has been the object of many investigations, but so far it has eluded explanation. Attempts have been made to analyse it from a chemical and electrical point of view, with no satisfactory result. It has been thought to be an electric force, but it was found to behave in a manner different from electricity. It has been recognized as a "force," but no one seemed to see where such a conclusion led. If it is a "force" and it does not correspond to any of the other forces recognized in nature, because it possesses peculiarities and properties of its own, then it is but logical to recognize it as a force as distinctive as gravitation, magnetism, or electricity.

If this be recognized, we can at once see how futile it would be to attempt a chemical analysis to find out its nature. Nobody would dream of such a procedure to find out the nature of gravitation. The way to investigate such a force is the method which has been pursued in regard to all the other known forces in nature. The enormous growth of the knowledge of the properties of matter has not come through the investigation of the forces in nature themselves, but in finding out the effects they produced. It is therefore evident that the only way this force can be investigated is by studying, not the impulse itself, but the effects which it produces.

The Impulse a Vital Force.

So far as this preliminary study of the subject has gone, we recognize that an impulse is the product of cell activity, that it can only be conveyed by living structures, and acts by stimulating cells to discharge their function. In being entirely related to living matter it differs from all other forces which have so far been recognized. Electricity, for example, with which it has been compared, can be conveyed by non-vital as well as vital structures.

In this inquiry it must be kept in mind that the effects which the force produces are the only evidences of its existence. The information to be drawn from these effects must be left to our powers of observation and reasoning, and this, again, must be guided by the results of experience. This being the case, the explanations which may be given at one time are provisional and must be continually revised, as experience sheds additional light upon the problem.

THE GENERATION OF IMPULSES.

In the primitive cell there exists in a rudimentary form the function of every highly specialized cell. Amongst these functions is that of producing impulses. This function is highly specialized in the cells of certain regions of the brain, and in a structure like the sino-auricular node of the heart. The function of impulse production is also possessed by other cells, notably by muscle cells. It is even present in the undifferentiated cells of plants.

The statement that impulses are the outcome only of cell activity is based upon the fact that they can neither be generated nor conducted without the presence of living cells. No cell can be stimulated into activity without the reception of an impulse or of some force which may produce the same effects as an impulse. The skin is a great sheet of cells, and these cells may be stimulated into activity by mechanical or other agencies. But the force which is conveyed into the interior of the body and which gives rise to the reactions, whether it be a sensation or the contraction of a muscle, is not the force which was applied to the skin, but is the impulse which such force caused certain cells of the skin to discharge. The impulses thus discharged were taken up by cells with parts specially evolved for the purpose, such as the receptors of afferent nerves.

Most of the organs of the body are never subjected to mechanical force, yet from every organ there flows a continuous stream of impulses. These impulses are generated by the cells of the organ. When a cell discharges its energy in the shape of its peculiar function it at the same time discharges an impulse. The human body provides innumerable instances. A hollow muscular organ is never at rest. Even in its most quiescent state its cells are continually passing into and out of activity, though its activity varies within

wide limits. The number of cells engaged in contraction may be relatively few, and little or no movement can be detected. At other times there is an increase in the number of cells participating in the contraction, and the contraction becomes stronger. A great number of cells may participate and a strong contraction of the organ may result. This can be shown in the case of a large full-time pregnant uterus. The hand placed over it may detect no signs of contraction, then at occasional intervals a slight hardening may be detected. At other intervals this hardening may be greatly increased, and there is no difficulty in recognizing that this variation in hardening is due to the increase in the number of muscle cells taking part in the contraction.

Coincident with these contractions we get ample evidence of the production of impulses. With the milder contractions there may be a slight increase in the pulse rate, a flushing of the face, and a slight degree of pain. When the contractions become more severe they are accompanied by a greater increase in the pulse rate, flushing in the face, and perspiration, pain of great severity, and an uncontrollable desire to bear down, with a suspension of respiration also, accompanied, it may be, with nausea and vomiting. Such phenomena, connected so clearly with the contraction of muscle, can only be explained by the generation of a great number of impulses produced by the muscle cells, taken up by the receptors of afferent nerves, and conveyed into the central nervous system, where they have reacted upon and stimulated the efferent nerves of the various organs concerned in producing all these phenomena.

If the skin of the chest be lightly rubbed with a piece of flannel, in some people a series of reactions follows. Two of the most striking are the appearance of a goose-skin (the pilomotor reflex) across the chest and down the insides of the arms, and at the same time the pupil dilates. Here the impulses from the skin have passed into the central nervous system and stimulated the sympathetic nerves which supply the pilar muscles and the dilator of the pupil.

Dr. Matland Ramsay has recorded another very striking illustration. In a case of iritis it was necessary to keep the pupil widely dilated, but atropine produced only a partial dilatation. The application of a blister at the side of the head or behind the ear produced complete dilatation of the pupil. As soon as the blister healed, the pupil became again partially contracted and atropine failed to produce complete dilatation. The blister was again applied. The pupil again became widely dilated. The raw surface was kept open and the pupil remained widely dilated.

The explanation is simple. The atropine causes dilatation by removing the influence of the constrictor muscle of the pupil on account of its action on the third cranial nerve. The removal of the influence of the constrictor pupillae was not sufficient to cause complete dilatation. The application of the blister generated impulses in the skin which stimulated the sympathetic and produced an increased contraction of the dilator pupillae, with a consequent complete dilatation of the pupil. The healing of the blister stopped the impulses; the renewal of the blister and the persistence of the raw surface kept up an increased flow of impulses and a constant stimulation of the sympathetic.

TONE AND THE VISCERO-MOTOR REFLEX.

When a voluntary muscle is at rest it remains in a slightly contracted state, giving rise to a firmness when it is palpated. When its nerve is cut the muscle loses its firmness and becomes soft and flabby.

The explanation of this change is that before the nerve was cut there was a continuous flow of impulses along the nerve, which, affecting but a few muscle fibres, kept the muscle in a state of mild contraction. The cutting of the nerve resulted in a cessation of these impulses and a consequent abolition of the contraction. This mild contraction is called tone.

While this description of tone may be accepted, the question arises, Whence come the impulses which produce it? It is manifest that the impulses must have a source. Clinical observation can throw a good deal of light upon the subject.

If the abdominal wall be carefully palpated in patients with an affection of an abdominal organ, the wall may be found hard and resistant (the visceromotor reflex), sometimes in limited areas, sometimes in more extensive areas, and sometimes the whole abdomen may be found hard and rigid. This has long been recognized, but no satisfactory explanation has been forthcoming. In some patients this hardness will be found to come and go with the worsening or improvement of the underlying morbid state, as in gastric ulcer and appendicitis. When it disappears it will be found to merge imperceptibly into the contracted state called tone, and when it increases it resembles an increase of tone. Indeed, there is little doubt that both conditions are due to the same cause—the tone being due to a few impulses reaching the muscle, while the hardening is due to an increase in the number of impulses.

Evidence of a similar kind is found in the "rigidity" of joints. In some patients the shoulder-joint may be so fixed that no movement can be obtained. If the patient is put deeply under chloroform the muscles relax and the joint can be moved with ease. The movement may elicit a grating sensation, evidently produced by a disease of the articular surfaces. As the effects of the chloroform pass off the rigidity returns. It is evident that the inflamed joint was the source of the impulses which caused the rigid contraction of muscles.

Reasoning from such facts as these, we conclude that the impulses which maintain tone are produced by the cells of the viscera or of the joint, and that the impulses from a particular source reach a particular muscle or group of muscles. The recognition of this increased contraction affords the clue to the seat of disease, inasmuch as the increased impulses are the result of disease. Further, as only certain diseased states produce these impulses, it may be possible to recognize the nature of the disease.

THE CONDUCTION OF IMPULSES.

(a) Cell to Cell Conduction.

There are different ways in which impulses are conducted. They can be transmitted from cell to cell. This occurs in plants, as in the hairs of *Drosera*, and in primitive animals like the sponges, where there is evidently no specialized part concerned in the conduction or reception of the impulse. There are a number of instances in which this method of conduction occurs in the human body. The conduction of impulses which produce cutaneous sensations can only occur by this method until they reach the receptors of the afferent nerves, the cells in this instance being those which constitute the epidermis. It is likely that this is the method of conduction of impulses in the auriculo-ventricular bundle and its branches (Purkinje cells) and in capillaries.

(b) Conduction by Nervous Networks.

The best illustration of this method of conduction is in the medusa. In this animal the chief parts concerned in the generation and conduction of impulses and the regulation of the contraction of the muscle are (1) a number of sensory bodies at the margin of the bell; (2) an underlying network of nerve fibres connected at the outer margin of the bell with the sensory bodies; (3) the muscle layer of the bell.

For a long time Romanes's interpretation of one of his experiments upon the medusa held the field. He found that when he took a strip of the bell, cut in a zigzag manner so as to avoid the possibility, as he thought, of nerve conduction, on applying a stimulus to one end of the strip a wave of contraction spread through the whole strip. He reasoned from this experiment that the impulse for contraction was conveyed from muscle cell to muscle cell, without the intervention of any nervous apparatus. This observation and interpretation has long been used as one argument in favour of the myogenic doctrine of the heart's contraction, and of the manner in which impulses for contraction were conveyed in the heart.

The later experiments of Mayer have shown that this result was wrongly interpreted. Mayer has shown that such a strip of muscle consists of a muscle layer over a network of nerve fibres. If a part of the muscle be destroyed so that there is a gap in the strip and an impulse be started, the muscle contracts as far as the gap, and the contraction

is begun on the other side of the gap, and continued to the other end of the strip. On the other hand, if a gap be made in the nervous network, the muscle layer being left intact, the contraction, started at one end of the strip, ceases when it reaches the gap in the nerve fibres, and there is no resumption of the contraction at the other side of the gap. From this experiment Mayer draws the conclusion that the impulse of contraction is not conveyed by the muscle, but by the nervous network.

In another experiment Mayer cut out of the body a ring of tissue which he immersed in sea water. By appropriate stimulation he was able to start a contraction in this ring, which passed as a wave completely round and continued beyond the place of excitation, and went round and round without any additional stimulation. This "circus movement" would continue for weeks if the tissue was supplied with fresh sea water. Here again, if he made a gap in the muscle layer, the wave passed on uninterrupted, but when a gap was made in the nervous network the movement ceased on reaching the gap.

The peculiar nature of the impulse is revealed by another experiment. Mayer¹ cut out a ring of the bell as before, but left a strip of the bell attached to the ring. When the circus movement was started, each time the wave passed the strip a wave of contraction passed along the strip to its end. He then placed the ring in a solution containing magnesium chloride, leaving the strip in plain sea water. The magnesium had the effect of paralyzing the muscle. The circus movement was started, and each time it passed the strip the strip contracted. Gradually the circus movement became less till it ceased and no movement could be detected, yet the impulse passed round and round, as was shown by the contraction passing along the strip at intervals, evidently due to the impulse continuing to pass round the network.

FIG. 1.—Diagram of circus movement in portion of medusa.

(c) Neurone Conduction.

Under this term is described that form of conduction by individual neurones as distinct from the network form of conduction.

The neurone is a highly developed cell, and there are at least four different parts specialized for particular functions. There is the part concerned in (1) the reception of impulses, (2) in the conduction of impulses, and (3) in the discharge of impulses; while there is (4) the cell body, which does not

FIG. 2.—Diagram to illustrate the reception, conduction, and discharge of impulses.

take any part in either reception, conduction, or discharge of the impulses, but whose function is to preside over nutrition. In this respect we see that the dendrites, the axon process, and the terminal fibrils play the same part as the fibres of the network in the medusa. This development of the neurone has not been sufficiently appreciated, and, in consequence, a good deal of confusion exists with regard to its function.

The peculiar functional part of a neurone may be seated at a considerable distance from the cell body, as in the afferent neurones of the skin (Fig. 2). The receptors of these neurones are the specially developed part, so that if in experiment the nerve is cut their function is lost and cannot be investigated. On the other hand, efferent neurones of the vagus and sympathetic have their functional peculiarity in the fibrils at the periphery, so that if

their fibres are cut and the peripheral portion stimulated the functional peculiarity of the neurone can be exercised and investigated. This seemingly simple and obvious statement has not been appreciated.

There can be little doubt that there is a large afferent part of the autonomic system which has completely escaped experimental observation simply because adequate means for investigation have not been employed. It is manifest that if in an experiment the afferent nerve be cut stimulation of either cut end cannot reveal the peculiar function which is situated in the receptors. It is evident that other means must be sought to gain the knowledge of the functions of afferent nerves. This means will be afforded by the opportunities of the physician, for it is manifest that it is through his opportunities that a knowledge of the sources of the impulses can be recognized. It is these impulses which stimulate the receptors of the afferent neurones, and some of the more striking manifestations which they produce are the symptoms of disease.

This constitution of the neurone gives a definite direction to the conduction of impulses. In the intact body impulses can only be conducted when they enter the neurone by the part specially evolved for their reception, and they leave the neurone by the part specially evolved for that purpose. Hence it is that the impulse travels only in one direction—from receptor to the discharging end—and passes from neurone to neurone or to effector organ in a particular way. It is only by a study of the passage of impulses that we can obtain a knowledge of the function of the different parts of the nervous system.

Nerve Force.

The term "nerve force" has been applied to this vital force, the impulse. From the foregoing description it can be gathered that it is in no sense a "nerve force," the nerves being merely structures specially developed for its conduction. While it is the peculiar function of the cells of some part of the brain to generate and discharge impulses, other structures also do so, as already described, so that the impulse, then, cannot be looked upon as a force produced by any particular kind of cell.

The Passage of the Impulse when the Conductors are Damaged.

In the heart we find that impulses travelling along a structure like the auriculo-ventricular bundle act in a peculiar way. The bundle may be damaged either by disease or by experiment, so that only a few strands can convey the impulses, and for some reason they are delayed in passing this narrowed part, but when they get beyond the part they stimulate the whole bundle and produce a complete ventricular contraction.

The same peculiar activity can be shown in the conduction of impulses by the network of fibres in the medusa. If a strip of the bell be made, and a cut almost severs the strip into two, the impulses which cause contraction of the near portion pass over this narrow part and cause as complete a contraction of the part beyond.

In a nerve trunk the conduction may be reduced to a small part of the nerve at one part. The impulses which pass this small part cause a complete response in the part beyond, showing that the impulse did not lose by having to pass over a narrow strand of the nerve.

The Passage of Impulses through Unspecialized Tissues.

It is now well recognized that in the living body there is a force whose presence can be demonstrated by the use of sensitive electrical instruments, such as the "electrocardiograph." Hitherto this has been attributed to a "current of action" produced by the contraction of the heart, but beyond that nothing is known.

A "current of action" implies the presence of a force. As it appears only as a consequence of muscle contraction, we are justified in assuming that the "current of action" is nothing more nor less than one of the effects of the impulse, and that its transference into an electric force is but an example of the change of one force or the effects of one force into another, as when the effects of gravitation are changed into electricity. Some aspects of the

¹ Rhythmical Pulsation in Scyphomedusae. Papers from the Tortugas Laboratory of the Carnegie Institution of Washington, vol. i, 1906, p. 122.

conduction of impulses have been described. The manner in which they pass through the body to be taken up by the electro-cardiograph at the extremities is another aspect.

This faculty of traversing unspecialized tissues so long as they are living is illustrated by a striking experiment. If the peripheral end of a cut phrenic nerve of a dog be laid upon the dog's heart, the whole diaphragm contracts with each beat of the heart. The impulses pass through the pericardium to reach the cut nerve, and the pericardium, beyond being composed of living cells, is not specially evolved for the conduction of impulses.

In noting these instances of the conduction of impulses, we see that there is something peculiar about the force which distinguishes it from any other force. In observing the effects it produces we gradually began to realize that it demonstrates peculiarities in the behaviour of the tissues. In its passage through the tissues it does not necessarily stimulate them.

The fact that impulses are so universal and readily permeate all living tissues raises the question how it comes about that only certain organs are stimulated. This has led to a review of the activity of cells and their susceptibility to impulses, and it has shown that this susceptibility varies in a manner that enables their activity to be regulated so that all organs, when they respond to impulses, do so in a fashion which enables their functions to be performed in a well ordered, purposive, and effective manner.

This inquiry has resulted in the discovery that the reception of impulses is governed by the law of fluctuation. The graded character of the response of the effector organ to impulse and stimulation and inhibition are dependent on this law of fluctuation.

THE INTERPLAY OF IMPULSE AND CELL.

In our investigations into the reaction of cells we find that all responses, whether physiological or the symptoms of disease, can be expressed in the terms of impulses and the susceptibility of the cells to stimulation. Hitherto many terms have been accepted as explaining reactions, because of some superficial character of the end-result, without any appreciation of what was really implied by the term. Stimulation and inhibition are terms of this sort, which, beyond indicating a seeming increased or decreased activity of an organ, yield no explanation of the processes which brought about the result.

In the same way terms have to be invented which suggest the existence of structures which do not exist. The term "centre" is spoken of as a definite entity, whereas it is but a figment of the imagination, created for the purpose of providing an explanation of reactions whose nature is not understood. So far as we have gone we see that some concept requires to be evolved that will express what is meant by a centre, based on the relation of the impulse to the receptors of neurones.

When we deal with disease, this way of looking at the phenomena enables us to obtain a far clearer insight into the nature of ill health. Already a great many symptoms which had baffled explanation are now capable of interpretation, and it needs but an extension of our knowledge of the susceptibility of cells to impulse for a great advance along the whole front of the attack on disease.

This will be grasped if we consider what constitutes disease. Disease has been defined as the reaction of the body to an injurious agent. The reaction means the effect produced by impulses upon cells. Ill health and death are but the outcome of the relation of the impulse and the cell.

The absence of a clear understanding has led to the use of terms which do little more than surround the reaction with an air of mystery. Such terms as "anaphylaxis" and "immunization" are in common use, but all attempts to explain them simply result in developing hypotheses impossible of proof. The clue to the explanation is to be found in this relation of the cell to the impulse. In our research into digitalis we have shown that there were conditions of the heart when the pulse rate could be reduced by digitalis from 150 to 30 or 40 beats per minute. In some such patients the pulse rate might rise suddenly to 70 or 80 beats per minute, and increased doses of

digitalis be without effect on the pulse rate. In the terms of the bacteriologist, the patient had become "immune" to the "toxin" of digitalis.

Such a result was a mystery until it was shown, with an abundance of evidence rare in medicine, that the reaction to digitalis is due to the interplay between the impulse and the cell. There was also indicated quite clearly the reasons why such startling differences could arise, and there is every reason for believing that investigation on these lines will lead to revealing the nature of all those reactions which are to-day obscured by the use of a pedantic terminology, descriptive only of end-results.

CONCLUSION.

While immense progress has been made and is being made in the knowledge of inorganic matter, little advance has been made in the knowledge of living matter beyond the accumulation of an enormous mass of reactions or end-results. The reason for the great progress in the one case was due to the recognition of the forces in nature which produced effects upon inorganic matter. The reason for the lack of progress in respect of living matter has been the absence of a knowledge of a vital force comparable to those of gravity, electricity, and magnetism.

The recognition of this vital force permits the same lines of investigation to be followed which has yielded such a rich harvest in the inorganic world. Although our attempts have as yet achieved but a small measure of success, we see it needs but time and experience to obtain a great addition to our knowledge of both physiological and pathological processes which will enable us to understand the nature of ill health. Now that we see the interplay between the impulse and cell, and recognize the effects produced, we realize how the absence of this kind of knowledge has rendered it impossible to explore such fields essential to medicine as the great system of afferent nerves and the processes and structures concerned in regulating the functions of organs.

OCCLUSION OF THE POSTERIOR INFERIOR CEREBELLAR ARTERY.

BY

ALBERT RAMSBOTTOM, M.C., M.D.MANCH.,
F.R.C.P.LOND.,

PROFESSOR OF CLINICAL MEDICINE, VICTORIA UNIVERSITY OF MANCHESTER;
HONORARY PHYSICIAN, MANCHESTER ROYAL INFIRMARY;

AND

JOHN S. B. STOPFORD, M.D.MANCH.,

PROFESSOR OF ANATOMY AND DEAN OF THE MEDICAL SCHOOL, VICTORIA
UNIVERSITY OF MANCHESTER.

ALTHOUGH a number of cases of occlusion of the posterior inferior cerebellar artery have been reported, the symptom-complex manifested by this lesion is not yet widely known. This, together with the realization that these cases provide a unique opportunity for amplifying our knowledge of the functions of the tracts and nuclei found in the retro-olivary region of the medulla, renders it a duty to place on record the results of investigations of all patients suffering from this condition.

The patient described in this paper exhibited most of the typical features seen after obstruction of the posterior inferior cerebellar artery and also presented a few points of special interest.

Charles C., aged 64, whilst following his usual employment as a painter, became suddenly dizzy and experienced a "hot flush" in the left side of his neck and head. He did not lose consciousness and was able to summon his workmates to assist him, as he was unable to walk without support. Within a short time of the onset he complained of abdominal pain and suffered from vomiting, but neither of these symptoms persisted long. After being taken home in the ambulance and put to bed, he was seen by Dr. Moreland of Cheetham Hill, and was given soda and milk, when it was found that he was unable to swallow, the fluid returning through his nose. When admitted to the Manchester Royal Infirmary a week later he was still unable to swallow and complained of difficulty in coughing, and the dizziness prevented him from walking without support.