to check the production of this poisonous enolic group, which ultimately overwhelms the body. Insulin, on the other hand, strikes at the root of the mischief.

But it remains true that any increase in the hydrogen-ion concentration of the blood produces dyspnoea. It is the lactic acid which is formed from the breaking down of glycogen which causes us to be "out of breath" after strenuous exertion. Ventilation of the lungs is thereby increased and more oxygen is taken in which rebuilds the lactic acid into glycogen, oxidizing one quarter of it in the process. Thus the blood is restored to normal and we are no longer breathless. Similarly the dyspnoea of uraemic asthma is due to the failure to excrete acid sodium phosphate, and the resulting acidaemia may be temporarily relieved by alkalis. But a man may also be breathless at a high altitude without any exertion, and his blood will be found to be more alkaline than usual. Here the mere lack of oxygen due to its low tension in the atmosphere directly stimulates the respiratory centre, nervous tissues being the most sensitive to this lack. The resulting dyspnoea washes out CO_2 from the lungs so that the blood actually becomes more alkaline, a condition which the kidney tries to rectify by excreting more alkali. This type is seen clinically in the dyspnoea of heart disease, which is due to oxygen lack, largely the result of capillary stasis, which allows of more complete reduction of haemoglobin. It is therefore usually associated with cyanosis, but there need be no increased production of acid. Indeed, the increased pulmonary ventilation may actually produce alkalaemia. Clearly it is no use to give alkalis, therefore, in cardiac dyspnoea. If digitalis is not contraindicated on other grounds it should be tried, because a cardiac tonic will help to relieve capillary stasis and the consequent anoxaemia. With the same purpose in view oxygen should be given, and it should be given through a rubber catheter introduced through the nose into the naso-pharynx. The catheter is attached to a Wolff bottle containing warm water through which oxygen is bubbled. Given in this way it can definitely increase the oxygen saturation of the blood, as has been proved by direct examination of the blood removed by puncture of an artery; given in the ordinary way it has no such effect.

The conclusion of the whole matter may be briefly stated thus: when acidaemia is associated with dyspnoea, the acidaemia is the *cause* of the breathlessness; when alkalaemia and dyspnoea are associated the alkalaemia is the *result* of the dyspnoea. Recognition of these facts is of great importance in selecting the appropriate measures of treatment.

A PLEA FOR A CLINICAL PHYSIOLOGY.

BY

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It is universally recognized that physiology has been of the greatest assistance to medicine, although the investigations of the physiologist have been carried on without immediate reference to their practical application to medicine. His chief purpose has been to discover the nature of the various manifestations of life. From such investigations material has been provided which can be used in the practice of medicine. This has brought physiology into close relation with the practice of medicine, and physiology occupies an important position in the medical curriculum.

While recognizing the value to medicine of physiology, including the method of animal experimentation, and that the progress of medicine could not have been made without its assistance, the question nevertheless arises whether physiology, as understood to-day, adequately supplies the kind of knowledge which is required for the continuation of medical progress. While it has revealed many matters essential to medicine, can it be relied upon to give that intimate knowledge of living processes which is necessary for the solution of medical problems?

This question does not refer to academic physiology as a whole but only to that portion related to medicine. In discussing the matter it is necessary to deal with certain defects in knowledge, not to disparage experimental physiology, but to indicate how it can be rendered of greater value to medicine. The doubt as to the adequacy of physiology for medical progress arose from the following circumstance.

Physiology and the Reflex Arc.

At the St. Andrews Institute for Clinical Research we recognized that the knowledge of living processes at present available was not sufficient to enable us to understand the nature of the most common symptoms or the action of a single remedy. A great mass of symptoms had been accumulated, and, in place of merely adding to their number, we resolved to try and find the laws that governed their production. We recognized that all phenomena in nature are subject to certain laws, and that the symptoms of disease, being phenomena in nature, are therefore subject to such laws.

In the course of this inquiry we recognized that symptoms were, in the main, due to an increased or decreased activity of certain organs, which came about through an interference with those processes and structures which are concerned in regulating their activity. These processes are spoken of in physiology as "reflex," and we put forward the theory that symptoms were due to the disturbance of normal reflexes.

Shortly after this view was published I was informed by one or two physiologists that any physiologist could have told us that symptoms were produced in that way. But when the matter was looked into, it was found that no physiologist could possibly have given us this information, for the simple reason that physiology to-day cannot supply the knowledge of the processes and structures which regulate any single organ of the body, whether a simple structure like a capillary, or a voluntary muscle, or a hollow muscle, or a secreting organ.

Physiology and the End-result.

The academic physiologist is mainly concerned with end-results. An end-result is the outcome of a chain of events. The chain of events is represented by the activities of certain structures which are concerned in producing the reaction of the organ to a stimulus. When, for instance in an experiment, the sympathetic nerve, or the vagus, is stimulated, the physiological instrument records only a movement of the heart or the output of blood from the heart. Such records may be interpreted as an augmentation of the heart beat, or a decrease. But no information is afforded which will explain the manner in which these reactions are brought about. We know now that there is interposed between these nerves and the heart muscle a series of structures which are involved in the production of the end-result. It is the modification of the activities of these structures which results in the manifestations of health and the symptoms of disease. A knowledge of them and the part they play in the movements of the heart in health and disease is essential for the practice of medicine. The physiologist has provided the knowledge up to a certain point, and it is necessary for progress that a form of physiological investigation should be employed that will give us a deeper insight into vital activities.

The Principle of the Reflex Arc.

In our attempts to get a better knowledge of the nature of ill health and of disease, we sought for some principle which would guide us in our work. We adopted as a guide what we call the "principle of the reflex arc." This is based on the fact that the functional activity of organs is dependent upon impulses which are brought to them by nerves, or structures having the same function as nerves. *The origin of every manifestation of activity is therefore to be found in some structure other than that which exhibits the manifestation.* The application of the reflex arc involves the search for the structures concerned in the production of the manifestation.

Physiology of the Heart.

If the assertion were made that the explanation to-day of every cardiac reaction, however carefully recorded, is inexact, and in the majority of cases misleading, it would certainly not be accepted. Yet if the matter be carefully considered it will be found that it cannot but be true. If it be borne in mind that the structure which exhibits activity is regulated and controlled by impulses generated and conveyed to it by other structures it will be seen that to understand the activity of the heart those other structures must be recognized.

A description of the movements of voluntary muscles without any reference to the part played by nerves would be defective, and the explanations given of these movements would be mere guesswork, and wrong guessing at that. The muscle fibres of the heart whose movements are recognized are as definitely under control of the conducting system as the muscles are under the control of motor nerves. Yet in the interpretation of the movement of the heart the conducting system is either ignored or imperfectly recognized. Marey's observations on the frog's heart are quoted to-day in physiological textbooks as if they were beyond dispute. The interpretation of the early experiments on the vagus nerve still holds the field. As all these observations were made before the existence of the conducting system was known, this interpretation is bound to be defective. The fact that the vagus, when it affects the heart's rate or rhythm, does so only through its influence upon the conducting system, has not been appreciated. What little is known to-day of the conducting system is merely the result of some crude experiments, or a few clinical observations for the most part imperfectly understood.

The Law of "All or Nothing."

Probably nothing illustrates so well the need for a clinical physiology as the profound belief in the law of "all or nothing." This law is accepted to-day as an article of faith. As a matter of fact, it is an experimental result, and while true for the manner in which the heart contracts in response to artificial stimulation, it is not true for the heart contracting under normal conditions. This becomes evident if the manner of stimulation in experiment and in nature be considered. An electrical stimulus is one which Nature never uses. It spreads by any structure which is capable of conducting it, and in its spread it is not guided or regulated, but stimulates every susceptible cell which it meets. By this method of stimulation the heart may contract according to the law of all or nothing.

On the other hand, if we consider how the normal contraction is produced, it will be seen that the stimulus for contraction of the ventricle arises as impulses thrown out by the sino-auricular node. These impulses are not electrical in their nature, but represent a form of energy which is only produced by living cells, and capable of being conducted only by living cells. From the sino-auricular node they pass by structures specially developed for the purpose of their conduction. They reach the ventricle by the auriculo-ventricular bundle, and enter the ventricle at a particular part, and within the ventricle the bundle breaks up into a great number of branches which are distributed to every portion of it. Manifestly this arrangement implies that the contraction of the heart normally starts at a particular place, and that each part of the ventricle is stimulated to contract in a sequence which results in an effective emptying of the chamber. Moreover, there is evidence to show that the heart, like every other muscular organ of the body, only uses as many fibres for each contraction as the circumstances require. In other words, the contraction of the ventricle is governed by the alternating activity of its fibres—that is, by the law of fluctuation, and not by the law of "all or nothing."

The Law of Fluctuation.

We find evidences that justify us in stating that all organs are governed by this law of fluctuation. It is at present assumed that the reactions obtained by such forms of stimulation as electricity are normal reactions, whereas

the stimulus, being artificial, can only give rise to artificial results.

It is for this reason that the law of fluctuation has been missed, and such a law as that of "all or nothing" has been adopted. The former can never be recognized by artificial stimulation, so that it can safely be predicted that the true physiology of an organ, as distinct from experimental physiology, will never be understood until the law of fluctuation is applied to the interpretation of reactions.

The Importance of the Conducting System.

Although I have been an assiduous student of the heart as seen in physiology and in clinical medicine for over forty years, I had but a confused idea of the heart's movements until in recent years we evolved the principle of the reflex arc and the law of fluctuation. By the application of this principle and law to the interpretation of cardiac phenomena there has gradually been revealed a field of observation whose value it is impossible to overestimate, not for the interpretation of cardiac phenomena alone, but also of those processes which are concerned in every form of vital activity. The study in this manner of the sino-auricular node and the auriculo-ventricular node, more especially the latter, enables us to understand the processes of stimulation and inhibition. The description of these processes in physiological textbooks is so confused and incomprehensible that it is impossible to obtain a clear understanding of their nature. The observations on these two nodes as revealed by the disturbances found so frequently in clinical medicine provides an opportunity for investigating these processes in a manner afforded by no other structure in the body, nor by any experimental method. In a like manner the action of the vagus and sympathetic can be studied with much greater precision. Many movements of the heart which it is impossible to explain while our ideas are dominated by the law of "all or nothing" are now explicable by the law of fluctuation. The action of remedies such as digitalis may also be investigated with a particularity that opens up a new field in pharmacology.

This line of investigation holds out the possibility of throwing light upon many of the functions of the brain. Like the brain, the conducting system not only discharges impulses which produce definite reactions but it does this, as does the brain, so that the reaction is regulated and controlled to adapt it to a definite purpose. Inasmuch as the constitution of the conducting system is so much simpler, the vital processes become easier of observation, and from these simpler effects we can interpret the more complex effects in the highly developed nervous system. In fact, in one sense we might look upon the conducting system as a rudimentary brain of the heart.

The Afferent Nervous System.

The great bulk of symptoms are the results of impulses conveyed into the central nervous system by afferent nerves. Experimental physiology has given us a great deal of information about the efferent autonomic system because, by its methods of stimulation, a demonstrable result is produced, as in the contraction of a muscle or the secretion of a gland; but such methods usually fail to elicit a response when applied to an afferent nerve. The reason for this is that the peculiar functional part of an afferent nerve is situated at its peripheral field in the different organs. Section of the nerve and stimulation of either end fails to give its peculiar reactions. The clinical evidence of the presence of the afferent nerves is abundant. By the study of such a physiological event as the contraction of the parturient uterus we can recognize the stimulus which excites the afferent nerves and can detect the result in the pain, flushing, sweating, increased pulse rate, nausea, and vomiting which frequently accompany the uterine contraction. Such opportunities for investigating the afferent system of nerves are afforded by almost every organ of the body, and the physician and surgeon have ample opportunities for such investigations, did they possess some definite principle to guide them. To a great extent these opportunities have been lost since physiology was separated

from clinical medicine. The expectation that the academic physiologist could provide this kind of knowledge has obscured the path which medicine should pursue, so that the magnificent opportunities of the clinician are imperfectly utilized. The development of surgery, for instance, has opened up unrivalled fields for exploration. However valuable a modern surgical textbook may be as a record of manual dexterity, it is in another sense a monument of wasted opportunity. The inspiration of John Hunter and William Beaumont is sorely needed.

Pain.

The poverty of modern medicine in ideas or concepts is well illustrated by the attitude of the profession to pain—the most clamant, the most universal, and the most diagnostic of symptoms. Though it has been a matter of discussion and investigation for ages, by physicians, surgeons, and physiologists, yet to-day we are provided with nothing but a mass of guesses as to its nature and origin, while its diagnostic significance is barely appreciated. A condition like angina pectoris is a perennial subject for discourses and discussions, and these consist mainly of futile speculations. In the production of pain there are definite structures and processes involved, but what these are no one knows. If the matter be considered it will be found that one might as well attempt to make bricks without straw as to solve the problem of pain without this kind of knowledge. The sad part of the matter is that medicine has not advanced far enough to know how to set about the solution of a problem of this sort.

The Evil of Specialism.

One of the great hindrances to the progress of medicine is specialism. The specialist is of necessity a man with a limited experience, and this leads to a limited outlook. When his work is directed by others with a wider outlook he is invaluable. When the direction of an enterprise is in the hands of a number of specialists, failure is bound to follow, for there is no one with that wide outlook to recognize the kind and number of specialists required and apportion to them their appropriate tasks.

Education in medicine is to-day dominated by a body of specialists, and not one of them has had that wide experience of medicine which would enable the relative importance of the different subjects to be understood in order that the student be taught only that part of special subjects which is essential to him in his future work as a doctor. The consequence is, he is to-day forced to learn a vast amount of stuff that will never be of use to him, while many essential matters are left out of his education. Amongst many examples is the question whether a woman whose heart is in a dubious state will be able to undergo the strain of pregnancy. This is a problem requiring a certain kind of physiological knowledge, but the physiologist cannot provide it. The cardiologist never sees a woman in labour, and the gynaecologist knows little or nothing, or, what is worse, may have wrong information of the heart. And yet our educational authorities are incapable of appreciating what this state of affairs portends.

The Agent which Stimulates—the Cell Impulse.

The experimental physiologist knows a good deal about the force he employs when he uses electricity, and physicists have given much study to electricity as a force. It is imperative that more knowledge should be obtained of the form of stimulation which Nature employs, as it is one with which the physician and the clinical physiologist deal. I have elsewhere drawn attention to the fact that it is a form of energy having properties as peculiar and as distinctive as the forces of gravitation and of electricity. Such a force has no doubt in a measure been long recognized, and has formed a subject of speculation for centuries. Dr. Gregory, 130 years ago, commented upon these speculations in his day. Some considered the force a "trembling or vibration of the substance of the nerve"; others attributed it to a "subtle and very active fluid"; while "others had recourse to an universal aether." How far knowledge

has progressed since then can be inferred from the description given by modern physiologists, who refer to it variously as a "propagated disturbance," an "excitation wave," "electricity," an "adequate stimulus," "motor and sensory impulses," "proprioceptive," "nociceptive impulses," etc.

The employment of so many terms implies a confusion of mind, inasmuch as the terms are based upon the effect the agent produces and not upon the agent itself; so that a contraction of a muscle is described as indicating the presence of a "motor impulse"; pain indicates the presence of a "nociceptive impulse" or a "sensory impulse." One might as well describe a "vomiting impulse" or a "sweating impulse" or a "nausea impulse," when other evidences of activity are produced.

The matter is put in this way to show that the use of such terms indicates a failure to appreciate the distinctive peculiarities of the cell impulse. This impulse, being a force in nature, is as invariable as electricity; consequently the character of the reaction does not depend upon the impulse but upon the cells which it stimulates.

The Relation of Physiology to Pathology.

There exists a good deal of confusion concerning what is physiological and what is pathological. It is usually accepted that in ill health there is some pathological stimulus which is quite distinct from that which occurs in nature or in physiological conditions, and in consequence the academic physiologist is not concerned with the reactions of ill health as they are not supposed to be physiological.

As a matter of fact, what are called pathological reactions are nothing more nor less than an increase or decrease of normal reactions: no new agent is introduced. When the process of stimulation is better understood this will be realized. The agents of disease act only by increasing or decreasing the excitability of cells or by increasing or decreasing the number of impulses. The impulse itself is the same in health and in disease, and it is the force or form of energy which produces a reaction.

On the other hand, the force or energy which the physiologist employs in using electricity is an abnormal stimulus, one that Nature never employs, and in consequence the reactions are of a kind that Nature never gives. Attention has already been directed to this fact in explaining that the law of "all or nothing" is an experimental result, and that Nature never employs this law in the regulation of the activity of organs. When the physiologist employs other means, such as a chemical agent, or heat or cold, he is imitating exactly the methods of stimulation which occur in pathological states. The symptoms of disease are often the same as physiological reactions.

Speculation in Medicine.

A clinical physiology of the kind that I have in mind would do a great deal in preventing that wild speculation which even at this day renders medicine a subject of ridicule. If it be kept constantly in mind that no manifestation of the body, whether a movement, a secretion, or a sensation, can take place without the reaction of a cell to an impulse, it would stop a great deal of that use of vague terms which injures every department in medicine. Medicine has descended in a constant stream through many centuries, and the characteristics of bygone ages are still reflected in present-day medicine. In the past, when certain manifestations were observed, knowledge was so defective that explanations purely imaginary were employed. When a reaction was obtained an explanation had to be given, and this old method of guessing is still dominant. So firmly established is this method to-day that branches of medicine are based entirely upon it—such as psychology. The result is that the greatest authorities are not men with scientific minds but those with the most exuberant fancy.

But the same method is found in every department. The term "centre" is in universal use, and it is not realized that a centre is but a figment of the imagination. Such

terms as "cardio-inhibitory centre," "vasomotor centre," "vomiting centre," "respiratory centre" are in common use. The term seems to connote something that many people believe to be a definite structure. Such an idea having gained currency, it becomes the easiest matter to explain difficulties by evolving new centres, and even to divide them into numerous subdivisions. Thus, there is not only a respiratory centre, but an inspiratory centre, an expiratory centre, an apneustic centre, and so forth. We even find such expressions used as an increased "tone of the inhibitory centre," no one having the remotest idea what constitutes tone or inhibition or a centre. Other difficulties are overcome by inventing a "synaptic membrane" which gradually becomes endowed with remarkable attributes.

Such terms should be eschewed by the clinical physiologist and his ignorance should be freely acknowledged, because in that way the defects of knowledge would be recognized and strenuous attempts made to remedy them, in place of making suggestions that hide the defects.

The Science of Medicine.

It is now time that it was recognized that medicine is a subject dealing with natural phenomena, with aims and objects peculiar to itself, and requiring methods as distinctive as any other science. The impression is generally held that the introduction of the methods used in physiology, in chemistry, or in bacteriology tend to make of medicine a science. Nobody would imagine that the use of chemistry in botany tends to make of botany a science, nor can the chemist claim to belong to the scientific side of botany. Yet laboratory subjects such as chemistry, physiology, and bacteriology are sometimes spoken of as belonging to the "scientific" side of medicine, the implication being that the clinical side is not "scientific." It cannot be too strongly insisted upon that the assistance rendered by these subjects is of an elementary kind, and, though necessary, they cannot provide that knowledge which is required for the solution of medical problems. Medical science demands the carrying of investigation far beyond the reach of the laboratory worker. When the medical investigator has obtained sufficient knowledge to enable him to recognize the vital processes and living structures which are concerned in the production of ill health, he has just rendered himself able to carry scientific medicine into a higher level. The next step is to assess the value of the symptoms of disease. It is only by this kind of knowledge that the relative importance of symptoms is recognized. The doctor must be able to tell whether there is danger present, not only to life but to health, and clearly to recognize wherein the danger lies. It is only when this information is obtained that steps can be taken to combat the danger. This is also the first step to a scientific therapy, for without this kind of knowledge all forms of treatment, whether successful or not, will remain empiric.

CONCLUSION.

If experimental physiology is to benefit suffering humanity a supplementary physiology dealing with the normal activities and those produced by disease must be employed, and experiment should be guided by the needs of the clinical observer. To a physiologist who is also a clinical observer the kind of experiment that is required is bound to be much clearer than the somewhat blind endeavours that have characterized the attempts to solve clinical problems in the past.

If the kind of physiology which clinical observation can reveal be not acquired, most of the enterprises which are concerned in the solution of the problems of disease will result in failure, or achieve a measure of success not in proportion to the time and energy spent.

The knowledge of physiology obtained in this way is limited to explaining the derangements which result in ill health, and cannot of itself solve the problems of disease, but it is an essential adjunct. Until it is acquired the work of the bacteriologist, of the pharmacologist, of the biochemist, as well as of the clinician, will fall far short of attaining the objects of their endeavour.

C

THE ACTION OF QUININE ON PROTEIN METABOLISM, RESPIRATORY EXCHANGE, AND HEAT FUNCTION.

BY

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[Abstract.]

FEVER of some type and varying duration occurs during the course of many diseases, and its treatment forms a considerable part of the work of the medical man, particularly in the tropics. It may be met with as one of the specific fevers with a definite causative agent, or may occur merely as a symptom in the course of some other disease. As we are able to overcome the causative agent in but few cases, we are reduced in the larger number to do what we can to conserve the strength of the patient and reduce if possible the waste of tissue and energy. This we endeavour to attain through careful nursing and feeding, especially in the long-continued fevers, so as to supply if possible the greater part, if not the whole, of the patient's daily expenditure of energy and minimize the strain on his accumulated reserves. But it is better to cut down the waste of energy if we can instead of trying to make up for it by increased supply. In disease, apart from the direct injurious effects of the causative agent, the maintenance of a high body temperature for any length of time in itself involves a large expenditure of energy. It is questionable whether the rise of temperature is beneficial in itself, and it is reasonable to suppose that if we could get the whole course of a disease to run at a lower temperature the patient would benefit; some energy would be saved, and his chances of recovery would improve correspondingly.

A mere lowering of the temperature is not enough to attain our object, however, unless it is due to a lowered production of heat by the body; if the temperature falls from increased loss of heat only, there need be no corresponding economy of the energy reserve, although some saving doubtless occurs. The antipyresis is attained through (a) the use of cold or tepid water baths, or (b) the antipyretic drugs like antipyrine, salicylates, and quinine. Water baths abstract heat from the body directly, and as the heat-regulating mechanism is still active in fever, it responds by increasing the heat production, so that although the temperature is reduced the energy expenditure of the patient is not reduced in a corresponding degree.

The antipyretic drugs, with the exception of quinine, have also been shown to reduce the temperature by increasing heat loss, and the tissue destruction was not materially lessened and sometimes was increased by their use. In the case of quinine, on the other hand, no unanimity of opinion has been attained, but the prevailing view is that it diminishes the protein metabolism and lowers the excretion of nitrogen, so that it effects a saving in the nitrogenous tissue waste. Protein destruction is ordinarily understood to imply the oxidation of the non-nitrogenous moiety of the molecule, and its reduction ought to show itself in a fall in the consumption of oxygen. But quinine is said not to affect materially the oxygen intake. In explanation of this conflicting behaviour of the nitrogen metabolism and gas exchange the suggestion is made that oxidation is not the only source of heat, but that heat may be liberated by such changes as the cleavage of protein molecules, in the course of which urea is formed. According to one view, quinine hinders these changes and thus reduces the temperature. Its action, moreover, is supposed to be exerted directly upon the tissues and not through the intermediary of the nervous centres.

Quinine is used to a large extent in the treatment of fevers, even when not malarial in origin—in which it is recognized to act primarily against the causative agent—and if the above views could be firmly established by experimental results they would provide a strong argument in