# SCIENCE

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## THE NEW PHYSIOLOGY[1]

LOOKING back on the history of physiology we can see that there have been various turning-points in general physiological theory, and consequently in the trend of research. Particular discoveries or series of discoveries, often in allied sciences, have led to these turning-points.

The last great turning-point in physiology was about the middle of last century. Up till then it was generally held that in a living organism a specific influence, the so-called "vital force," controls the more intimate and important physiological processes. Inspired by the rapid advances of physics and chemistry, the younger physiologists of that time broke away from vitalism, and maintained that all physiological change is subject to the same physical and chemical laws as in the inorganic world, so that in ultimate analysis biology is only a branch of physics and chemistry.

The subsequent progress of physiology has shown that all, without exception, of the physical and chemical hypotheses then advanced in explanation of intimate physiological processes were far too simple to explain the facts; but the general conclusion that biology is only a special application of ordinary physics and chemistry became firmly established, and is still what may be called the orthodox creed of physiologists. It may be truly said that most physiologists look upon this creed as something which has been established for all time, and that they would be inclined to regard any deviation from it as harmful

[1] A lecture delivered before the Harvey Society, New York, October 14, 1916.

scientific heresy. Nevertheless I think that we have again reached a turning-point, and that a new physiology is arising in place of the physico-chemical physiology which has held sway for so many years. I propose in this lecture to give some account of how, as it seems to me, this new physiology is shaping itself.

It is natural for us to assume that the aim of all investigations in physiology must be to ascertain the causes of physiological activity. However complex a physiological reaction may be, the conditions which determine it can be investigated experimentally; and from long experience we can be quite certain that such experimental investigation will always lead to some result, however obscure. There is, and can be, no limit to experimental investigation of causes. When, however, we examine the results obtained by experimental physiology there emerges a point in which they differ greatly from the results ordinarily obtained in the investigation of inorganic phenomena: for it is characteristic of physiological reactions that they are dependent to an extreme degree on all sorts of environing conditions. We recognize this when we speak of stimulus and response rather than of cause and effect. When the light from a star is focused on the retina there is a physiological response by night, but none by day. The response evidently depends on the existing state of excitation of the whole retina. It also depends on the normal nutrition of the retina and brain. If the blood is abnormal in composition the ordinary response is interfered with; and we are as yet only at the beginnings of knowledge with regard to the minute changes in blood composition and other conditions of environment which are sufficient to affect the response very materially.

It is the same with every physiological response. The further we investigate the more evident does it become that each physiological response depends on a vast number of conditions in the environment of the responding tissue. On superficial investigation we do not realize this: for we can often get exactly the same response, time after time, with the same stimulus. To the attainment of this result it is only necessary to see that the conditions are "normal." It is only after more thorough investigation that we find that "normal conditions" imply something which is both extremely definite and endlessly complex. We then begin to realize that the maintenance of normal conditions is from the physical and chemical standpoint a phenomenon before which our wonder can never cease.

Physiological investigation of causes seems, thus, to lead us up to a tangled maze of causal conditions. He who looks for definite "causal chains" in physiological phenomena finds in place of them a network of apparently infinite complexity. The physiologists who led the revolt of last century against vitalism did not see this network. To them it seemed that there were probably simple physical and chemical explanations of the various physical and chemical changes associated with life. The progress of experimental physiology since that time has effectually shown that this was only a dream, and physiologists are now awakening from the dream.

But we are also awakening from another dream. About the middle of last century it seemed as if, in the current conceptions of matter and energy, we had reached finality as regards the inorganic world. The chemical atom, on the one hand, and the energy associated with it, on the other, seemed to represent bed-rock reality—a reality including not merely inorganic, but also organic phenomena. Discoveries connected more particularly with electrical and electro-chemical phenomena, the periodic law, and radio-activity are awakening us from this dream also. The supposed bedrock reality of a former generation seems to be melting down before our eyes. The solvent has been the study of particular phenomena, such as those of radio-activity. The professional physicists and chemists have hitherto kept away from the serious study of life. For the most part they have regarded life as something apart: or as a complex physical and chemical phenomenon which is not likely to throw any light on the deeper problems of physics and chemistry. In this attitude I think that they have been mistaken; but in any case it is evident that we must guard against the quite unwarranted assumption that the only possibility of advance in physiology is by the direct application to life of the physical and chemical ideas which held unchallenged sway for so many years.

In this reference I should like to reply to some remarks, made partly with reference to my own writings, by my friend Professor Macallum of Toronto, in a very able and interesting presidential address to the American Society of Biological Chemistry two years ago.[2] After frankly admitting that the apparent difficulties of the mechanistic interpretation of life "put a task upon the human spirit which is apparently not imposed thereon in the theoretic explanation of any other department of science" he proceeds to argue that this is because "our knowledge of the laws that operate in matter is as yet only a very remote approximation to the whole of the lore on this subject that is possibly attainable and that will be ultimately attained." He feels, however, that this defence of the mechanistic theory is somewhat dangerous, and therefore proceeds to point out "that though we know so little of the properties and laws of matter, we know it with a degree of certainty which is not exemplified in the case of any other department of the known or the knowable, and further that the most rational method of interpreting vital phenomena is to explain the unknown in terms of the known, to trace back the causation of the obscure and mysterious to the operations of wholly natural laws and processes."

Now with this latter sentiment I am in entire agreement; but I would point out that Professor Macallum had just invoked not what he considers the known, but, on the contrary, the totally unknown properties of matter, to furnish us with a future physico-chemical explanation of life. I confess that there is in his argument a certain theological smack which strongly appeals to me as a fellow Scotchman. In the domain of "Apologetics" he would, I feel sure, make a great impression. But in the domain of Natural Science we have to examine arguments somewhat closely, and it seems to me that his admissions, which are right and unavoidable, carry him so far that his defence of the mechanistic theory of life is wholly unconvincing. One can not get round the fact that the mechanistic theory has not been a success in the past, and shows no sign of being a success in the future.

When we look broadly at biological phenomena, it is evident that they are distinguished by one universal characteristic. The structure, activity and life history of an organism tend unmistakably to maintain a normal. Accident may destroy an organism, or even a whole species, but within limits of external environment which are the wider the more highly developed the organism is, the normal life history of each individual is fulfilled.

[2] *Journal of Biological Chemistry*, XVII., p. VIII., 1914.

If, now, we consider the advance of physiological knowledge from the standpoint of the efforts which have been made, not to ascertain the causes of vital activity, but to track out its normal details, the past history of physiology takes on a new aspect. It becomes a record, not of disheartening repulse before a hopeless wire entanglement, but of continuous progress. The new physiology of which I wish to speak to-night is a physiology which deliberately and consciously pursues this line of progress, leaving on one side what one may call the "causal" physiology handed down to us from the last generation. This new physiology is in one sense not new, but very old. It is only new in the sense of consciously pursuing an aim which has nearly always been instinctively pursued by physiologists, and particularly by the great physiologist from whom this society takes its name.

Now I think that many of my hearers will at once say that such a course may be useful up to a certain point, but that it is not true science, and that therefore we can not desert the old attempts. We must, in fact, still continue our frontal attacks on the wire entanglement. To this criticism I shall endeavor to reply later. But meanwhile I should like to explain more clearly, and by means of examples, what the new physiology aims at.

Perhaps I can do this most directly by referring first to the corner of physiology which has largely occupied my own attention—the physiology of breathing.

When we count the breaths, or measure their depth, we find much irregularity, as if there were no very definite or exact regulation of the breathing. Any active occupation, such as speaking or singing, interferes in various ways with the breathing, and the impression at first produced is that the regulation of breathing is very rough. It is also commonly believed that by special training we can increase, or "improve," the ventilation of the lungs. On the other hand it has been well known for long that the breathing is more or less regulated to correspond with the consumption of oxygen and production of carbon dioxide in the body. Thus during heavy muscular exertion greatly increased breathing accompanies the greatly increased oxidation in the tissues. Another fact, well known to physiologists, is that if the lung ventilation is by artificial or voluntary means greatly increased for a short time, there follows a period of "apnea," during which natural breathing is absent. The exact cause of this apnea was till recently obscure. In 1868 Hering and Breuer showed that the inflation of the lungs in inspiration gives rise to impulses passing up the vagus nerves, and inhibiting further inspiratory impulses from the respiratory center, at the same time starting expiration. Deflation of the lungs in expiration has a converse effect. So long as the vagi are intact they are constantly playing this game of battledore and shuttlecock with the respiratory center, and Hering called this the "self-regulation" (Selbst steuerung) of breathing. The apnea following excessive ventilation of the lungs was interpreted by subsequent physiologists as the summed inhibitory effect of repeated distentions. Fredericq showed, however, that apnea is produced when the respiratory center of one animal is supplied with blood from another animal the lungs of which are excessively ventilated. This, therefore, is a true "chemical" apnea, due to over-aeration of the arterial blood, and was distinguished from "vagus" apnea. Nevertheless the correlation of the various "factors" apparently involved in the regulation of breathing remained extremely obscure.

I observed that when the air breathed is gradually and increasingly vitiated by rebreathing it, or by what is known to miners as "black damp," the breathing is also increased, but not in any simple relation to the extent of the vitiation. With a steady increase in the vitiation the breathing at first increases only a little, but as the vitiation increases further the effect on the breathing is greater and greater. Thus an increase from 4 per cent. to 5 per cent. in the percentage of $CO_2$ in the inspired air produces about 20 times as great an effect on the breathing as an increase to 1 per cent. from the normal of 0.03 per cent. Observations of this kind suggested that the breathing is so regulated as to maintain a certain normal percentage of carbon dioxide in the air within the lungs, and that as the percentage in the inspired air rises a greater and greater increase in the breathing is required to maintain this normal. It is, moreover, excess of carbon dioxide that excites the breathing. A corresponding deficiency of oxygen has no such effect.

It was found by Mr. Priestley and myself that a sample of the air in contact with the blood in the lungs could easily be obtained by catching the latter part of the air expired in a deep inspiration. As we expected, the percentage of carbon dioxide in this air turned out to be on an average practically constant for each individual.

If the frequency of breathing is voluntarily varied, even as widely as from three a minute to 60 a minute, the depth adjusts itself so as to keep the average alveolar percentage of carbon dioxide almost absolutely steady; and conversely if the depth is varied. With resistance to breathing there is a similar effect. The effort put into inspiration and expiration is so increased as to overcome the resistance and keep the alveolar carbon dioxide almost steady. If the breathing is temporarily interrupted or abnormally increased, the time is made up afterwards, so that the average alveolar carbon dioxide percentage is practically steady. If, finally, the inspired air is vitiated by carbon dioxide, the breathing is so increased as to keep, if possible, the alveolar percentage approximately steady.

The effects discovered by Hering and Breuer appeared to them to depend simply on the state of mechanical distention of the lungs, and to have no relation to the chemical regulation of breathing. Mr. Mavrogordato and I have quite recently reinvestigated these phenomena in man. The results showed that the amounts of inflation or deflation needed to produce the Hering-Breuer effects depend entirely on the chemical stimulus of carbon dioxide. When this stimulus is absent, as in apnea, a very slight inflation or deflation will suffice, so that the breathing is, as it were, jammed during apnea; while if the chemical stimulus is strong it needs a great inflation or deflation to produce the Hering-Breuer effect. The vagi prevent useless prolongation of inspiratory or expiratory effort and consequent waste of time in breathing, or damage to the lung structure. They also coordinate the discharges of the center with actual inflations or deflations of the lungs. When the vagi are cut the breathing becomes slow, and, as Scott showed, can only imperfectly respond to an increased chemical stimulus, since the frequency can not be increased. The influence of the vagi is entirely in the direction of keeping the alveolar air normal. Perhaps nothing illustrates more clearly the dependence of nervous reactions on more fundamental physiological conditions than the varying response of the respiratory center to the stimulus of inflation or deflation of the lungs.

When excessive ventilation of the lungs

is so arranged that there is no fall in the alveolar percentage of carbon dioxide, no apnea follows. There is thus no such thing as the so-called vagus apnea. Apnea is simply due to excessive removal of carbon dioxide from the alveolar air.

When the barometric pressure is varied it becomes evident that the normal which dominates the regulation of breathing is not the percentage of carbon dioxide in the alveolar air, but the partial pressure or molecular concentration. At the normal atmospheric pressure of 30 inches there is about 5.6 per cent. of carbon dioxide in the alveolar air, but only 2.8 at 60 inches barometric pressure, and 1.4 at 120 inches. In these three cases the percentage of $CO_2$ varies widely, but the partial pressure is the same. It is only with constant barometric pressure that the normal percentage is steady.

When the breathing is increased by excess of $CO_2$ in the inspired air, or increased production of $CO_2$ in the body, there is, as might be expected, a slight rise in the alveolar $CO_2$ percentage. It is this slight rise that is the stimulus to increased breathing. Roughly speaking, a rise of 0.2 per cent. increases the resting breathing by 100 per cent., while a fall of 0.2 per cent. produces apnea. The stimulus of the increased $CO_2$ percentage is conveyed to the respiratory center by the blood. Under ordinary average conditions the center responds with normal breathing when the blood leaving the lungs is saturated with air containing 5.6 per cent. of $CO_2$, but does not respond at all when the blood is saturated with 5.4 per cent. of $CO_2$ or less. The threshold value of $CO_2$ is, however, greatly lowered by excessive administration of acids or in any condition of so-called acidosis, and is raised by alkalies or an alkaline diet. This and other evidence points to the fact that $CO_2$ acts on the respiratory center in virtue of its acid properties when in solution.

According to modern ideas the acidity or alkalinity of a liquid depends on its hydrogen ion concentration. The accurate measurement of the hydrogen ion concentration of blood by the electrometric method is attended with great difficulties; but these have been to a large extent overcome by Hasselbalch of Copenhagen, who has obtained measurements of the effects of saturation with different partial pressures of $CO_2$ on the hydrogen ion concentration of blood. He has also shown experimentally that when the alveolar $CO_2$ threshold is lowered or raised by an acid or alkaline diet this raising or lowering is just sufficient to keep the hydrogen ion concentration of the arterial blood sensibly steady. It is now certain, therefore, that what the respiratory center is reacting to when it reacts to a slight increase in the alveolar $CO_2$ percentage is the consequent slight increase in the hydrogen ion concentration of the blood.

The latter increase is so minute that it can only be detected electrometrically when it is of sufficient extent to produce very gross changes in the breathing. The respiratory center is enormously more delicate as an index of change in hydrogen ion concentration of the blood than any existing physical or chemical method.

As already remarked, the alveolar $CO_2$ percentage is extremely steady under ordinary resting conditions. This implies that the hydrogen ion concentration of the blood is regulated with almost incredible delicacy, and must be so regulated apart altogether from the breathing. The breathing simply regulates the rapid disturbances in hydrogen ion concentration caused by variations in the production of $CO_2$: other disturbances are regulated otherwise than by the breathing. There is clear evidence that both the kidneys and the liver play a part in this regulation; but of the marvellous accuracy of the regulation physiologists had, till the recent work on the physiology of breathing, no clear conception.

It is not merely the hydrogen ion concentration of the blood that is accurately regulated, but also its capacity for taking up a constant amount of $CO_2$ in presence of a constant partial pressure of this gas. This capacity depends on the concentration of and balance between alkaline salts and albuminous substances in the blood. Recent investigations by Christiansen, Douglas and myself have shown that this concentration and balance are so accurately maintained day by day, and month by month that under normal conditions no deviations can be detected by the most delicate existing method of blood gas analysis. The balance can be temporarily upset by what may be called violent means; but within an hour it is back again to normal. It is, of course, evident that if the carrying-power of blood for $CO_2$ did not remain normal the breathing and circulation would not, without special adjustment, remain normal.

Now let us look back for a moment, and see where we now stand. The experimental study of the physiology of breathing has led us to the discovery of four normals, the maintenance of which furnishes the interpretation of a mass of what would otherwise be isolated and unintelligible observations. We have first of all the normal alveolar $CO_2$ pressure. This turns out to be directly subordinate to the normal regulation of the hydrogen ion concentration of the blood, the normal reaction of the respiratory center to hydrogen ion concentration, and the normal regulation of the capacity of the blood for carrying $CO_2$. With the discovery of each of these normals we have obtained deeper and deeper insight into the physiology of breathing. We have done this, not by merely seeking for causes in the physical sense, but by seeking for interconnected normals and their organization with reference to one another and to other organic normals. These normals represent, not structure in the ordinary physical sense, but the active maintenance of composition. We may fitly call this living structure, since so far as we know all living structure is actively maintained composition, the atoms and molecules entering into which are never the same from moment to moment according to the ordinary physical and chemical interpretation. Our method has thus been essentially the same as that of the anatomist who seeks for the normal—the type—which runs through and dominates the variety of detail which he meets with, and who reaches more and more fundamental types.

I wish, now, to point out that the same method has been applied, and is being applied, to other departments of physiology, even though the physiologists applying it may have failed to realize the far-reaching significance of their results.

I will refer first to the general physiology of the blood. The facts that the hydrogen ion concentration and capacity for carrying $CO_2$ are very accurately regulated in the blood are no isolated facts in physiology, although the accuracy of our physiological means of measurement renders them peculiarly striking. Claude Bernard, in his *Leçons sur les phénomènes de la vie,* was, I think, the first to point out clearly that the composition of the blood, as well as its temperature, is physiologically regulated. He was led to this conclusion more particularly by his observations that in prolonged starvation there is still sugar in the blood, and that even when great excess of sugar is introduced into the body the percentage in the blood remains very steady, as excess is taken up by the liver and other organs, or excreted by the kidneys. Voit's observations on the relative constancy of the sodium chloride in the blood, and the manner in which the kidneys regulate this percentage, are of a similar character. If food freed from chloride is administered the elimination of chloride by the urine diminishes to almost nothing, though the high percentage of chloride in the blood-plasma remains about the same. As Voit also showed, the blood during prolonged starvation retains its normal composition, and its volume remains proportional to body weight, while other tissues (*e. g.*, muscle) are reduced.

Dr. Priestley and I have recently investigated the excretion of water by the kidneys. By simply drinking large quantities of water one can produce an enormous increase in the secretion of urine, and this urine is almost pure water. What we wished to observe was the degree of watering down of the blood which was necessary to produce the huge increase in excretion of water. We did not doubt that the watering down would be very small, but when we attempted to measure the dilution by determining the percentage of hemoglobin we found that there was no dilution at all, though the method used was one of extreme accuracy. When, however, the plan of measuring the electrical conductivity of the serum was adopted, a slight, but quite distinct, diminution in the conductivity could be detected during, and ending with, the diuresis. This showed that there was a slight diminution in the salt-concentration, and to this diminution the secreting cells were reacting. Here, then, we are in presence of another exactly but elastically regulated normal, the slightest deviation from which produces, in the kidneys, a reaction comparable in its exquisite delicacy with the reaction of the respiratory center or liver or kidneys to a change in hydrogen ion concentration.

The physiology of the kidneys has, in accordance with prevalent physiological conceptions, been attacked from the side of "causal" explanation. I know nothing more hopeless than the attempts to explain the outstanding features of secretion of urine on the lines of ordinary physics and chemistry. So far as the facts are yet known we can, however, get a practical grasp of the kidney activities if we attack the subject from the standpoint of the active maintenance of the normal blood composition.

Let me turn now to the general physiology of nutrition. In the preliminary stages of investigation of this subject physiology has owed much to the pure chemists, and this debt is constantly increasing. We have only to think of the work of such men as Black, Priestley, Lavoisier and Liebig. Like Wöhler, who synthesized urea, Liebig was a convinced vitalist. For him there was a central kernel of vital activity under the control of the "vital force"; but outside this central kernel he interpreted the phenomena of nutrition on purely chemical lines. He thought of oxygen as something free to oxidize anything oxidizable within the body, except what is protected by the vital force; and he assumed that the greater the concentration of oxygen in the lungs, and the greater the supply of food-material to the body, the greater will be the amount of oxidation, since only a limited amount of oxidation is under the direct control of the vital force. He gave special attention to the elimination of urea and other products of nitrogenous oxidation, and introduced methods of measuring the nitrogenous waste. It was found, apparently in direct confirmation of his general ideas, that the amount of urea excreted rises and falls, except for a certain starvation minimum, in direct proportion to the amount of albuminous food eaten. The excess over the starvation minimum was looked upon as "luxus consumption"—an ungoverned oxidation, due to simple chemical factors.

But the matter was soon carried further by the physiologists—particularly by Pflüger, and by Voit and his pupil Rubner. It was found that, other conditions being equal, the consumption of oxygen is within wide limits independent of the abundance of its supply, and that the actual consumption of oxygen per unit of body weight is very little different during starvation from what it is when abundant food is supplied. In starvation more fat is being oxidized to compensate for the deficiency in albuminous oxidation. Finally, the brilliant work of Rubner established the fundamental fact that within very wide limits different food substances are simply substituted for one another within the organism in direct and exact proportion to the energy which they furnish when broken down. The energy liberation per unit body weight is practically constant, but if excess of food is taken the excess of potential energy is stored up as fat and glycogen, while if food is withheld the stored excess is used up. Even when all the stored fat and glycogen is used up, the organism finally flings its own living structural substance into the balance, and in this last desperate effort to maintain the normal metabolism the nitrogenous oxidation again rises to an amount which for a short time compensates for the energy previously yielded by fat. When death from starvation at length comes the old flag—the flag of life—is still flying.

The massive work of Atwater and his pupils on human nutrition, in which it was shown that the normal daily food requirement of a man is about 3,500 calories in energy-value, was of course a direct extension of the idea of normal nutrition. We maintain an energy consumption of about 3,500 calories, just as we maintain about 5.6 per cent. of $CO_2$ in our alveolar air, or hemoglobin of 18.5 per cent. oxygen capacity in our blood, or legs of a certain length and anatomical structure. By a strange confusion of ideas the idea is abroad that nutrition is a matter of simple chemistry and physics, and that when we estimate food values in calories, we are exemplifying this fact. This is enough to make a staunch old vitalist like Harvey or Johannes Müller turn round in his grave and laugh. What is it in the body that measures out or withdraws protein, carbohydrate and fat with meticulous accuracy in terms of their energy value, in such amount as to maintain the normal energy metabolism? Is it not the vital spirit or vital force? the old physiologists would ask. Is not this phenomena of a piece with all the other distinctive phenomena of life, and ought not physiology to face these phenomena fairly and squarely and generalize from them, not run away from them? This is the question I am trying to put to you now.

Now I wish to make it clear that it is not vitalism, but simply biology, that I am preaching. Vitalism is a very roundabout and imperfect attempt to represent the facts. Physiological study, and biological study generally, seems to me to make it clear that throughout all the detail of physiological "reaction" and anatomical "structure" we can discern the maintenance of an articulated or organized normal. This idea brings unity and light into every corner of physiology. In other words, it helps us within limits to predict, just as the ideas of unalterable mass and energy help us within limits to predict, or the ideas of time and space help us within limits to predict. I claim nothing more for it, but also nothing less. The idea of life is just the idea of life. One can not define it in terms of anything simpler, just as one can not define mass or energy in terms of anything simpler. But this one can say—that each phenomenon of life, whether manifested in "structure" or in "environment," or in "activity," is a function of its relation to all the other phenomena, the relation being more immediate to some, and less so to others. Life is a whole which determines its parts. They exist only as parts of the whole.

At first sight it might seem as if it must be very difficult to make use of this conception as an instrument of research: for evidently we can not investigate the parts without investigating the whole. The difficulty is only apparent. The whole is there, however little we as yet comprehend it. We can safely assume its presence and proceed to discover its living details piece by piece, in so doing adding to our knowledge of the whole. If, on the other hand, we attempt to take the organism to pieces, or separate it from its environment, either in thought or in deed, it simply disappears from our mental vision. A living organism made up of matter and energy is like matter and energy made up of pure time and space: it conveys to us no meaning which we can make use of in interpreting the facts.

But is there not matter and energy in a living organism? Do we not assume this at every step in physiology? We make use of the ideas of matter and energy in biology, just as the physicist makes use of the idea of extension in the investigation of matter. To the biologist, however, the structure and activity of an organism are no mere physical structure and activity, but manifestations of life, just as to the physicist the extension of matter is no mere mathematical extension, but a manifestation of the properties of matter, with a physical and not a mere mathematical meaning. This is the answer to those who point to the dependence of physiology on physics and chemistry, and conclude from this that physiology can not be anything but a department of physics and chemistry. By a similar chain of reasoning physics would be nothing but a branch of mathematics, and mathematics itself would melt away into that universe of unconnected "impressions" which David Hume imagined, but Immanuel Kant showed to be non-existent.

The limits of time prevent my giving further examples of the light which the conception of the normal throws on the details of every part of physiology, and I must now try to probe more deeply. It may be pointed out that although it is useful in matters of detail to bear in mind that a living organism tends to maintain a normal of both structure and activity, and to pass through a normal life history, yet in ultimate analysis all this *must* be due simply to the reactions between its structure and physical and chemical environment. I will not at this point quarrel on general grounds with the "must," but simply endeavor to test it by the facts of physiology.

We can distinguish in a living organism what seems a more or less definite structure of bony matter and connective tissue. Yet we know that all this is built up, and in adult life is constantly being pulled down, rebuilt and repaired, through the activities of living cells. It is thus within the living cells that we must look for the structure which is supposed to react so as to maintain the normal. These cells are made up of what has been called "protoplasm." Now the more we study protoplasm the more evident does it become that this "substance" is extraordinarily sensitive to the minutest changes in environment. Take away or diminish or increase the minute traces of calcium or potassium salts in the blood-plasma, or the traces of various substances supplied to the blood by other organs; or add traces of certain other substances: the reactions of the protoplasm are quickly altered, and its structure may be destroyed. It is evidently in active relation with its environment at every point, and one can not suspend this activity without altering it. Even deprivation of oxygen for, perhaps, a minute may kill a nerve-cell. There is no permanent physical structure in the cell: the apparent structure is nothing but a molecular flux, dependent from moment to moment on the environment.

Now when we look at the blood, the internal or immediate environment on one side of the cells in the body, we find, as already shown, that this is almost incredibly constant in composition. Were it not so the reactions of the cells would become chaotic, and their structure would be completely altered if not destroyed. But the constancy of the blood is maintained by the combined reactions of the organs and tissues themselves. The intimate structure of the living cells depends on the constancy of the blood, and the constancy of the blood depends on the intimate structure of the tissues. If we regard this condition as simply a physical and chemical state of dynamic balance, it is evident that the balance must be inconceivably complicated and at the same time totally unstable. If at any one point in the system the balance is disturbed it will break down, and everything will go from bad to worse.

A living organism does not behave in this way: for its balance is active, elastic, and therefore very stable. When a disturbance affects its structure or internal environment it tends to "adapt" itself to the disturbance. That is to say its reactions become modified in such a manner that the normal is in essential points maintained. An injury heals up: destroyed tissue is reproduced, or other parts take on its function: the attacks of microorganisms are not only repelled, but immunity to future attacks is produced. In reproduction the body periodically proceeds to renew almost the whole of its structure. Death may be regarded as a periodical scrapping of structural machinery, and reproduction as its complete renewal.

The Anglo-American expedition of which I was a member studied, on the summit of Pikes Peak, Colorado, adaptation to the want of oxygen which causes, in unadapted persons, all the formidable symptoms known as "mountain sickness." As adaptation proceeded the blueness of the lips, nausea, and headache completely disappeared, and it was then found that even during rest the lung epithelium had begun to secrete oxygen actively inwards. The kidneys and liver were now also regulating to a lower degree of alkalinity in the blood, so that the alveolar $CO_2$ pressure was diminished, and the breathing consequently increased, thus raising the oxygen-supply to the lungs. There was also a marked increase in the hemoglobin percentage and in the blood volume. The organism had so adapted itself as nearly to compensate for the deficiency in oxygen supply, just as a heart gradually compensates for a permanent valvular defect.

The normals of a living organism are no mere accidents of physical structure. They persist and endure, and they are just the expression of what the organism is. By investigation we find out what they are, and how they are related to one another; and the ground axiom of biology is that they hang together and actively persist as a whole, whether they are normals of structure, activity, environment or life history. In other words organisms are just organisms and life is just life, as it has always seemed to the ordinary man to be. Life as such is a reality. Physiology is therefore a biological science, and the only possible physiology is biological physiology.[3] The new physiology is biological physiology—not bio-physics or bio-chemistry. The attempt to analyze living organisms into physical and chemical mechanism is probably the most colossal failure in the whole history of modern science. It is a failure, not, as its present defenders suggest, because the facts we know are so few, but because the facts we already know are inconsistent with the mechanistic theory. If it is defended it can only be on the metaphysical ground that in our present interpretation of the inorganic world we have reached finality and certainty, and that we are therefore bound to go on endeavoring to interpret biological phenomena in the light of this final certainty. This is thoroughly bad metaphysics and equally bad science. It is the idea of causation itself that has failed, and failed because it does not take us far enough. We have not at present the data required in order to connect physical and chemical with biological interpretations of our observations; but perhaps the time is not far off when biological interpretations will be extended into what we at present look upon as the inorganic world. Progress seems possible in this direction, but not in the direction of extending to life our present every-day causal conceptions of the inorganic world.

I now wish to add a few words as to the relation of physiology to medicine; for I am one of those with an intense belief in the intimate connection between the two sciences, and it seems to me that the mechanistic physiology of the nineteenth century has failed to take the rightful position of physiology in relation to medicine. What is the practical object of medicine? It is to promote the maintenance and assist in the reestablishment of health. But what is health? Surely it is what is normal for an organism. By "normal" is meant, not what is the average, but what is normal in the biological sense—the condition in which the organism is maintaining in integrity all the interconnected normals which, as I have already tried to indicate, manifest themselves in both bodily structure and bodily activity.

Now for the mechanistic physiology there are no interconnected normals, just as in the inorganic world as at present interpreted there are also no interconnected normals. If we look through an average existing text-book of physiology we find a great deal about the effects of this or that stimulus, a great deal also about the external mechanism and chemistry of bodily activity—a great deal, in other words, about what lies on the surface but never takes us further. Along with this there are perhaps also some inconclusive discussions of the possible mechanism of such processes as physiological oxidation, secretion, growth, muscular contraction, or nervous activity. Very little will, however, be found about what in reality lies still more on the surface, but also penetrates deep down—the maintenance within and around the body of normal organized structure and activity. The maintenance of the normal is something for which there is no place in the mechanistic physiology, since according to this physiology maintenance must be in ultimate analysis only an accident of structure and environment—a fitful will o' the wisp which does not concern true science.

But medicine, as we have seen, is supremely interested in the physiological normal. What a man sees at the bedside is

[3] It has been suggested to me that if a convenient label is needed for the teaching upheld in this letter the word "organicism" might be employed. This word was formerly used in connection with the somewhat similar teaching of such men as Bichat, von Baer and Claude Bernard. *Cf.* Delage, L'Hérédité, Paris, 1903, p. 436.

a perversion of the normal, and nature's attempts to restore it, with what assistance medicine can give. For medicine it is necessary to know the normal in its elastic and active organization. He who knows how the body regulates its normal temperature will not confuse heat-stroke with fever, or make the mistake of attributing fever to mere increased heat-production in the body. He who knows how the breathing is normally regulated will be in a position to distinguish at once between various causes of abnormal breathing; and similarly for every abnormal symptom met with in disease. But the mechanistic physiology gives a minimum of information about the regulation of the normal. One looks in vain in physiological text-books for connected accounts of the regulation of breathing, circulation, kidney activity, general metabolism, nervous activity. The main facts of physiology are partly ignored, and partly strewn about in hopeless disconnection and confusion. A student of medicine may learn some true physiology at the bedside, or he may never learn it at all, and become either a hopeless empiric or what I do not hesitate to call a mechanistic pedant.

Medicine needs a new physiology which will teach what health really means, and how it is maintained under the ordinarily varying conditions of environment. We also need a pathology which will teach how health tends to reassert itself under totally abnormal conditions, and a pharmacology which will teach us, not merely the "actions" of drugs, but how drugs can be used rationally to aid the body in the maintenance and reestablishment of health. The new physiology, new pathology, and new pharmacology are growing up around us just now. I can see them more particularly in the splendid advances which the medical and other biological sciences are making in America. You have the advantage of having less of old intellectual machinery to scrap than we have in the old countries; but perhaps we shall not be much behindhand.

If we look on pathology as simply the description of damage to bodily structure, and the analysis of the causes of this damage, then pathology may be very helpful in preventive medicine, but does not help much in therapeutics. When, however, pathology studies the processes of adaptation to the unusual, defence of the organism against the unusual, and reproduction of the normal, just as the new physiology studies the maintenance of the normal under ordinary conditions, then therapeutics and surgery will be aided at every step by pathology, and a rational biological pharmacology will have its chance.

Sometimes one hears the complaint that the world has grown old: that the great discoveries have all been made; and that nothing is left to us now but to work out matters of sheer detail. Perhaps the great and constantly growing mass of rather uninteresting, but otherwise apparently meritorious scientific literature, increases this impression. At certain moments one may long for the past centuries when there was much less to read, and people seemed to have plenty of time to think, and to have endless material for new discoveries and projects. But in reality I do not think that there was ever more scope for new ideas and discoveries than there is at present. Among the new ideas are those of the new physiology, the outlines of which I have tried to trace in this lecture. Those who do not feel inclined to accept this new physiology, or who are still sceptical as to its theoretical basis, will, I hope, at least make allowance for any personal failure on my part to present it to them in a more convincing form.

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