Thermodynamics in Physiology.[1]

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UNIVERSAL APPLICATION OF PHYSICAL LAWS.

FORTUNATELY for physiology, several of the generalisations of science appear to be strictly true, even when applied to the living organism. Although such exact experiments are not possible on man, or animals, or plants, as may be made on non-living objects, there is little evidence—indeed, I would be bold and say there is no evidence—that such living creatures can, in any manner or degree, evade the ordinary laws of mechanics, chemistry and physics, the principles of the conservation of energy and mass. At intervals we hear stories of table-turning, of levitation, of ghosts shifting the furniture around, of so-called " electronic " reactions for diagnosing disease, of spirit photographs, of homœopathic medicines which can cure in concentrations about equal to that of a single molecule dissolved in the visible universe. If one is liberal-minded one occasionally examines the evidence —a disheartening process and subversive of liberalism ; it is generally of the kind which requires a dark room, incense, and holy music, or a medium who is too shy to answer criticism, or a stream of special cases, or a faculty for explaining away all the examples which do not confirm the theory.

There really is *no* evidence that momentum and kinetic energy, that chemical transformations, that electrical and magnetic phenomena, occur in the living body in any manner, or to any extent, which differs from that obtaining in the more readily investigated non-living world. It is true that physics and chemistry are still only skimming the surface of the world of natural phenomena. No doubt we shall find new theories necessary, new limitations, new corrections, new adaptations of old theories. It is probable that in the very simple tasks (my words are intentionally provocative) which lie before them, physicists and chemists will always attain a much higher degree of exactness than we poor physiologists—even had we their skill—could aspire to, when investigating the very refractory and fugitive objects which Nature supplies. No doubt the faint-hearted, or those with a preference for the miraculous, will still be at liberty to assert that the generalisations of physics and chemistry have not been proved to apply to the material manifestations of the living creature. We can at any rate answer that they have not been proved *not* to apply, and that our function, or profession—or calling—is to apply them ; we cannot, and we do not if we are reasonable, predict what the result will be ; but we continue to face the future with hope.

The transformations of matter in the living creature and the chemical dynamics of living events are the study particularly of biochemists. Their task is more messy, more difficult, than that of their cousins—or shall we say uncles—the chemists ; there is no evidence, however, that it does not rest on precisely the same basis. The transformations of energy are the study of biochemists and physiologists alike. If we study the exchanges of energy in living creatures or cells, we find, not indeed with the same precision as in physics and chemistry, but with cumulative evidence, that these exchanges also rest on precisely the same fundamental laws as in the other sciences. Not many will dispute the application to the living cell of the principles of conservatism of energy and mass ; few would suppose that, by taking thought, one could add either a cubit to one's stature or a kilowatt to one's output. These principles can be, and are, accepted. Philosophically speaking, the Second Law of Thermodynamics, dealing with the limitations of the availability of energy, is more liable to doubt. It is known to rest on a statistical basis, and when we are dealing with units, complete, self-reproducing, yet as invisible and intangible as the filter-passing or other micro-organisms, it is, theoretically speaking, possible that some means may be available of evading the statistical relations which govern the behaviour of larger systems. But here again we must ask for evidence—and there is none of a precise and definite character which suggests, in the least degree, that the living cell can escape the jurisdiction of the Second Law.

THE MEANING AND SCOPE OF THE SECOND LAW OF THERMODYNAMICS.

The Second Law is a statement of the limited " availability " of energy. In physiology the unit—the living cell—with which we deal is so small that we may safely regard it as a purely isothermal system. This makes the statement of the law much simpler. In any isothermal system there exists a quantity called the free energy, which is, mathematically speaking, a single-valued function of the co-ordinates of the system ; when the system is isolated in an infinite isothermal medium, any reaction which goes on in it will tend to diminish the free energy ; when the system passes from one state to another, the loss in free energy A is equal to the maximum external work which the system could have done in the change ; in a position of equilibrium the free energy is a minimum. The maximum work is very seldom, if ever, attained. That fact need not disturb us. The conception of the maximum external work enables us, by means of imaginary, though reasonable and consistent, reversible changes, to calculate the free energy, that quantity which we know to exist as a single-valued function of the co-ordinates of the system. Furthermore, if we imagine our system to be warmed up, but otherwise unaltered except by such consequential changes as of pressure and electromotive force, the maximum work A of any given process will be increased or diminished, according to the equation $dA/dT = Q/T$, where T is the absolute temperature and Q is the heat absorbed in the process.

FREE ENERGY IN THE CELL.

The living cell requires energy to carry out its processes ; how can it get this energy ? The plant can

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store radiant energy by means of chemical synthesis; apart from this, however, there is no evidence that any cell can obtain energy by other than chemical means. Now energy, in itself, is of no particular value; what the animal needs is provision for carrying out movement, for growing and reproducing, for secreting and excreting, for transmitting impulses, for correlating reactions, for purposeful or intelligent response. It requires the means of doing external or internal work: *it requires free energy.* A reaction which can release much heat, but can do little work, would be of no particular value to animals. Perhaps for that reason the reactions which animals employ, namely, oxidations of the ordinary food-stuffs, appear to yield a large proportion of free energy; their maximum work is of the same order of size as their total heat. Hence the animal, or the cell, on its ordinary diet, is not likely to be deprived of the means of doing work; it has plenty and to spare; the limits to its "efficiency"—if we may use that word for the ratio of work done to total energy used—are set, rather by the irreversible nature of its processes, by the friction in its parts. In calculating the maximum work we have to suppose that our changes are very slow, that they are without friction, that no leakage occurs, that a small alteration in the conditions would send the machine equally well in the opposite direction.

IRREVERSIBILITY OF LIVING PROCESSES.

Such a state of affairs does not obtain in the living cell. More important considerations than "efficiency" and reversibility, in the thermodynamic sense, have played their part in evolution: quickness and readiness of response, a strict and specific inheritance of bodily and chemical structure, the precise maintenance of an internal medium ensuring continuity and individuality, all these have proved far weightier factors than the need of conserving energy. An animal might be efficient thermodynamically—this would profit it little if a bigger, quicker, less economical but more powerful animal came and ate it up. Hence, when we consider the whole cycle of an animal's behaviour, we find a relatively poor utilisation of its energy. A frog's muscle never shows an actual working efficiency of more than 10 per cent. of the total energy which it liberates in contraction; it never turns more than 10 per cent. into work; the remaining 90 per cent. appears as heat—and is wasted, for the frog has no use for the heat. Had it learnt to employ reversible processes, it might perhaps have attained an efficiency of about 100 per cent.; but then it would have been the more likely—after digestion—to provide energy, less efficiently maybe, but more quickly for some one else. Even man, whose food supply is a more urgent and insistent problem, never attains an efficiency higher than 25 per cent. It is far more important, biologically, to be a better man in a fight, in a struggle with Nature, in captivating or capturing the other sex, than it is to approximate to a condition of thermodynamic reversibility.

It would seem, therefore, that a consideration of the actual thermodynamic efficiency of living processes is not likely to lead us far. There may be creatures, very possibly there are, the conditions of whose lives make possible a closer approximation to the type of process which we call reversible. Indeed, it is conceivable that cells can exist in which a means is available of bettering even a reversible process. A one-sided, selective permeability, maintained by an active, "purposeful," but molecular mechanism in the cell, something like Maxwell's demon with his trap-door, might enable the cell to evade the statistical rules which govern larger systems. Philosophically, perhaps even practically, the discovery of such a mechanism, if ever made, will be the greatest step taken by science; if life and matter are co-equal and co-eternal, as some believe, it may be that life is maintaining the entropy at a reasonable constant level, to enable the universe to evade the dilemma of a finite future and a finite past. But, alas, there is no evidence. All the processes which living cells are known to conduct are wasteful and inefficient, very far from reversible. In the thermodynamic sense they are fully representative of a viscous, leaky, inefficient, wasteful—not to say a wicked—world. The Second Law leads us nowhere yet in that direction.

APPLICATION TO LABILE EQUILIBRIA.

The most striking verifications and applications of thermodynamic reasoning occur in quite another direction, namely, in connexion with what are called labile equilibria. The free energy is employed, not for its own sake, but to enable us to calculate the conditions of equilibrium. Many and varied are the equilibria which occur in the living cell and body—and hence the importance of the Second Law. The equilibrium of water with its vapour, of a solution with the vapour of the solvent, of an acid with its ions, of the ions on two sides of a membrane, of chemical bodies in an interface, such are simple examples of the application of the Second Law.

Consider such a simple thing as a blood corpuscle. A membrane, permeable to water and oxygen and carbon dioxide, to some ions, but not to others, filled with a complex solution of hæmoglobin and salts: much too large and sober to be able to evade the Second Law; much too small, however, for us to examine individually by any available physical or chemical technique. This corpuscle is in equilibrium; it exists, at any moment, in a reasonably steady state; its surface indeed is so large, relative to its mass, that a new equilibrium is attained (when the conditions alter outside) with sweeping rapidity. We do not know exactly what the conditions of equilibrium are. We have permeability and impermeability; we have charged and uncharged bodies in solution; univalent and multivalent ions; electrostatic forces, and electrical potentials; precisely the conditions which require thermodynamic treatment. There cannot, I insist, be much real understanding of the nature of the equilibrium at the surface of such a cell without a thermodynamic basis. We do not know the cause of the impermeability and permeability of the cell envelope; maybe it is a matter of solubility in a fatty film. We do not know the molecular constitution of many of the reacting bodies; probably we shall some day. From the point of view of thermodynamics, however, such details are inessential. Given the actual facts, of permeability and impermeability of the membrane, of valency and "activity" of the reacting ions, certain conclusions are inevitable; the conditions of equilibrium are defined.

Electrical Phenomena in the Cell.

Almost every manifestation of activity in a living cell is accompanied by a change of electrical potential, sometimes slow, often very rapid. These electrical potentials are relatively large: they may reach several hundredths of a volt; in certain organs indeed, *e.g.* in the electric organ of Torpedo, they may amount to many volts, though here it is supposed, in order perhaps to put less strain on one's credulity, that the units are linked up in series, like a high-tension battery, to produce an enhanced effect.

These electric changes have long provided one of the chief, perhaps the chief, of the physical problems of physiology. They were attributed at one time to living electromotive molecules—whatever those might be: that was before the days of thermodynamics; then to diffusion potentials such as those described by Nernst as existing at the contact of two different solutions. Unfortunately no diffusion potential possible in the body, strong acids and alkalies being out of the question, could be nearly large enough to explain the potential differences actually observed; all the ions available in any quantity have much the same mobility, and the positive and negative ions destroy each other's effects. To avoid this difficulty Beutner has suggested, much as Bernstein did before him, but with stronger physico-chemical evidence, that these electromotive changes are due, fundamentally, to just the same causes as operate in the case of the glass electrode—the highly specific permeability of a membrane by one ion.

Thermoelastic Phenomena in Muscle.

The study of the heat-production of muscles has led to interesting results of many kinds, in regard to the working of the muscular machine. These results imply and require the First Law of Thermodynamics, that of the Conservation of Energy; usually, however, they do not introduce the Second Law, and it is better perhaps to retain the term "thermodynamics" for studies in which both laws are applied. The application of thermodynamics in this stricter sense to muscle physiology is made in a curious and unexpected way.

If a piece of ordinary metal wire be stretched its temperature falls; if it then be released its temperature rises again. The process can be made reversible, and the result may be deduced, by thermodynamical reasoning, from the known facts concerning the thermal expansion of metals. Other substances show the same phenomena. If an india-rubber strip be stretched its temperature rises; if it be released its temperature falls. These results are the converse of those with metal—a corollary of the fact that the coefficient of thermal expansion of rubber is negative. In the case of rubber, however, the process is not strictly reversible in the thermodynamic sense; in the complete cycle a certain amount of heat is lost, owing to the internal friction, the viscosity of the rubber; only if the stretch and the release be infinitely slow will thermodynamic reversibility be attained. Similar phenomena are shown by inactive muscle, alive or dead: stretching warms, and releasing tends to cool it; in the complete cycle, carried out infinitely slowly, the total effect is nil.

These phenomena are not small and unimportant; it is conceivable, indeed likely, that they play a part in the sequence of thermal events known to occur in active muscle. The trouble, however, about an active muscle is that it is so very unsuitable a medium for studying reversible cycles; the force due to its activity is like the pressure exerted in a bombardment by inelastic particles, it is caused by a rapid succession of completely irreversible events. It is probable, nevertheless, or at least possible, that so long as the muscle is retained in a constant state of activity by a rapid succession of shocks, each of which liberates a certain known amount of energy, it may be regarded as a fit vehicle for thermodynamical reasoning: certainly—to take an analogy—a leaky rubber balloon, kept filled to an exactly constant degree by an electric blower, would provide a reasonable—if not a satisfactory—object on which to study the laws of expansion of a gas. That, alas, is the kind of object—a leaky rubber balloon—which we poor physiologists have to employ when we try to make accurate observations and to think precisely!

Now it has recently been found by Fenn that an active muscle allowed to shorten and do work, requires an extra amount of energy, about equal to the work done, over and above the much larger amount required to set up and maintain its activity. Conversely, stretching it causes it to absorb some of the heat released as a result of the stimulus. Shortening causes a liberation, lengthening an absorption of heat; the exact converse of the process which occurs in a resting muscle or an indiarubber strip, but the analogue of that which happens in a metal wire. Can it be that the much less extensible body, the active muscle, has quite different thermoelastic properties from the more extensible one, the resting muscle? May we suppose that the coefficient of thermal expansion of active muscle is positive, while that of inactive muscle is negative? Unfortunately it is impossible to try experimentally; the experiment would take too long; the state of activity would have passed away and the muscle would have become fatigued; and probably the rise of temperature would have its effect, not only on the length of the muscle, but on the magnitude of the individual explosions, the resultant of which is the state of activity as we see it. The problem is an obscure one, but it is difficult at present to see any explanation of the thermal phenomena produced by stretching and releasing an active muscle, unless they be thermoelastic in their nature.

The difficulty is enhanced by further observations made on a muscle while it is undergoing the physiological process known as relaxation. When the stimulus to a muscle ceases it relaxes, its state of activity disappears at a certain definite rate. If it be allowed to lengthen under a load, to lower a weight, in relaxation, there is an extra production of heat, over and above that which would occur if it relaxed unloaded. Conversely, if it be hindered from shortening throughout the contraction, and then released and allowed to lift a load only during relaxation, the extra production of heat will be negative, the total heat will be less than if it relaxed unloaded. Lengthening during relaxation causes a production, shortening during relaxation an absorption of heat. If we are to explain this on thermoelastic grounds we need a negative coefficient of thermal expansion during relaxation, a hypothesis which one can see no means of testing experimentally. Yet, unless we accept the thermoelastic explanation of both sets of phenomena, we are reduced to attributing them to "Nature," or to some unknown "adaptations" inherent in the cell—in other words, to admitting that we can give no kind of rational solution of the problem.

FUNDAMENTAL DIFFICULTIES OF PHYSIOLOGY.

This is the kind of difficulty with which, as physiologists, we have to deal. Our problems are prescribed for us. We cannot sit down and invent a reversible cycle, we cannot investigate some special and simplified case of our own choosing. What would a student of thermodynamics say if his machine had perforce to have food and drink and oxygen, to prevent it from collapsing while he put it hurriedly through its Carnot cycle? How pleased would he be with an elastic body which had one set of properties at one moment, another set at another? What accuracy would he attain if his membranes began to leak as soon as he deprived them momentarily of oxygen? There are very fundamental difficulties in our way. These difficulties cause some of us to become careless, many of us to become pessimists; some of us to perform bad experiments, all of us to make bad theories; some to affirm, as an act of faith and on insufficient evidence, that living cells are nothing but ordinary electrons and atoms, to deny the existence of that fundamental organisation which is called "life" by wiser and more commonplace folk; others, equally perverse, to attribute it all to "Nature" and to the inherent "adaptability" of the cell.

Amid all these difficulties and perversities, these bad experiments and these bad theories, it is something to have a reasonable point of support. Thermodynamics may be hard to understand, but not so hard as the living cell; it may be an imperfect tool, but it is better than none: and it enables us often to evade the part which we do not understand in the mechanism of the cell, to draw conclusions directly from observed fact, and to predict the consequences of phenomena which we may not understand but of the existence of which we are sure. Conjecture and surmise, imaginative thought, are required of such as would adventure in physiology, as in any other science: a method, however, which can yield certain results, can allow precise deduction, as thermodynamics properly applied can do, even though comparatively seldom, is an invaluable asset in a study such as physiology, where, at present, alas! so little is surely known, so little is susceptible of exact and logical analysis.

Physiology, which is beginning to claim its place as an exact science, can learn much from Joule's work. From the first Joule appreciated the value of accurate measurement: precise measurement, precise definition, more than anything else, are the present needs of physiology. In his day the study of electricity was just emerging from the indefinite state of any early science: physiology is just emerging from that state now.

SUMMARY OF LECTURE.

There is no good evidence that the ordinary laws of physics and chemistry, including those of thermodynamics, do not apply to the living cell and animal. When proof to the contrary is alleged it is always found to be of the kind which requires a high degree of credulity, an emotional preference for the miraculous, an imperfect appreciation of the canons of scientific thought, or an ignorance of the actual principles involved. The First Law of Thermodynamics—that of the Conservation of Energy—has been shown, directly and indirectly, to apply to living cells and bodies, with an accuracy equal to that of any experiments which may be made to test it. The Second Law, that which deals with the availability of energy, is more difficult to test, but there is no evidence of any value that it also does not hold. The Second Law is founded, in principle, on a statistical basis; it deals with the average behaviour of systems containing very many fundamental units. It is conceivable that the ultimate minute mechanism, especially of the smallest living cells, may somehow be able to evade the statistical rules which govern larger systems; it may, for example, like Maxwell's demon, be able to sort molecules, to utilise the energy of the more rapidly moving, to employ a uni-directional permeability, and so to avoid the general increase of entropy which appears to be the governing factor in all other material change. Such an evasion, if established, would be of ultimate philosophical, biological, and practical importance; there is no evidence, however, of any value, that it really occurs.

The free energy, the maximum work, of a system undergoing an isothermal change is a mathematical conception which is of little direct importance in physiology; the conditions of an animal's existence render its transformations of energy very far from "reversible" in the thermodynamic sense. It is valuable indirectly, however, since it enables one to predict the characteristics of the many labile equilibria which are present everywhere in the body and cell, without properly understanding, or even being aware of, their ultimate nature. In a subject so difficult, experimentally and theoretically, as physiology, a method which has such certainty of application as that of thermodynamics should appeal, as G. N. Lewis says, to all those who, while they do "not wish to reject all inferences from conjecture and surmise . . . will not care to speculate concerning that which may be surely known." The method of thermodynamics enables us to draw definite and quantitative conclusions from accurately observed facts, even though we know nothing of the mechanism involved.

The lecture dealt with the characteristics of several equilibria occurring in the body or cell. The potential differences at interfaces, the properties of systems involving indiffusible ions, the principles of electrometric measurement, certain properties of colloidal solutions, and the various equilibria occurring in blood during the cycle of respiration, were discussed from the point of view of thermodynamics. The curious thermal effects associated with stretching, or releasing, an elastic body also were discussed, and applied to some recent observations on the behaviour of contracting muscles. Finally the lecturer, "as in pious duty bound," referred to the great influence which Joule had exerted on all such work as had been discussed, and pointed out that the guiding principles in the life and labours of this great citizen of Manchester—those of precise measurement and accurate definition—are the essential needs of physiology at the present time. The hour would come when physiology would demand its Einstein, its Maxwell, its Laplace; to-day, however, physiology requires a Joule—a dozen Joules—to carry out the accurate measurement, and to formulate the precise definitions, which are essential if it is to secure its promotion from the nursery of observation and wonder to the schoolroom of exact science.