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THE GUTHRIE LECTURE.

Some Problems of Living Matter.

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BEING THE SECOND GUTHRIE LECTURE.

I AM, I understand, to discuss to-day physical problems raised by the study of living matter. There is no lack of such problems. I am embarrassed by their number and variety.

Let me begin by some general account of living matter. A simple single-celled animal of the type of *amœba* has a volume roughly equal to a sphere of about 30μ radius. It is composed of a translucent turbid material showing no structure. Recently such cells, in spite of their minute size, have been dissected while still living. The operation was carried out under the microscope with fine needles of hard glass, operated by a mechanical device. The result has been to remove some classical misconceptions. One is that living matter has a foam structure. Dissection shows that the appearance of spaces filled with fluid is due to the presence of fat drops, which can be dissected out of the living cell. Such drops are probably merely food reserve, and are external to the living substance. The latter, freed from such masses, is in some places a rigid gel, in others a fluid of high viscosity—that is to say, a slime. Somewhere in the cell is a mass having distinctive properties called the nucleus. It may be either a colloidal solution enclosed in a very tough membrane of transparent gel, or a tough gel containing many granules from 0.5μ to 1.5μ in diameter, which is rigid in the sense that minute pieces broken off do not round up under the influence of molecular attraction. The living substance is sometimes a puzzling combination of fluidity and elasticity. This is especially the case with the substance of a muscle fibre. A glass needle may be moved about in it in all directions freely, but if a portion be broken off it can be pulled out into a filament of extraordinary length, which when released will almost regain its previous shape.

The ordinary microscope, therefore, teaches us only that the actual living substance when freed from food matters and stored chemical products is a translucent gel or slime. The ultra-microscope carries us a stage further. It shows the translucent material to be composed of an optically homo-

geneous substance, in which are embedded a multitude of minute particles. Usually the particles are in Brownian movement; the mass, therefore, as a whole is more fluid than solid. But the Brownian movements sometimes cease for a time, to be renewed later. The degree of fluidity, therefore, is variable, the mass, or portions of it, may alter in the direction of a rigid gel, and the change can be reversed. Such a change in the direction of an increase in rigidity seems to entail the expenditure of energy, since it is described as occurring in response to an external stimulus. It is also characteristic of the death change when the free energy of the cell runs down with rise of temperature.

The appearance of minute particles shown by an ultra-microscope is common to colloidal systems, so we may in general regard the living cell as a mixture of colloidal slimes of varying degrees of fluidity. This seems a curiously insufficient basis for the prodigious potentialities of, *e.g.*, an ovum or spermatozoon!

One feature may suggest more to my audience than it does to myself—namely, that though the substance of the living cell is uniformly translucent to light of ordinary wave-length, some parts are remarkably opaque to ultra-violet light. This is true of the nucleus. By taking advantage of this difference, quite sharp photographs have been obtained of the nucleus in the living cell.

The activities of these simplest organisms are at first sight as simple as their structure. Consider, for instance, their mode of progression. It is no more than a flowing of the protoplasm which causes the whole cell to roll along a surface. A few grains of charcoal placed on the upper surface of an amoeba are carried forward—*i.e.*, in the direction of motion of the whole animal over the forward edge and backwards along the face in contact with the surface over which it is crawling. It reminds one of Helmholtz's account of the displacement of electricity when a dielectric is rubbed over a surface. The simple movement of an amoeba is what would occur if the contact potential difference between the animal and the solid were greater at the front than at the back end.

At intervals the animal takes into its interior particles of food by flowing over them. It dissolves out the portion profitable to itself and extrudes the remnant. But this seemingly purposeful act is very closely copied when drops of chloroform in water are fed with particles of glass coated with

shellac. The particles are pulled into the interior of the drops, the shellac dissolved and the indigestible masses of glass thrust out.

We have merely to observe the marvellous variety of animal and plant life to realise that this appearance of simplicity must cover a real complexity. The appearance of simplicity is, indeed, but an example of the characteristic of living matter, the adaptation of the means to the end. The phenomena are simple only so long as the object to be attained is simple. Take movement as an example. I have watched one of these simple cells endeavouring to bend and break a chain of bacteria so as to get short lengths capable of being ingested. During the operation a particular cell became extended between the ends of a chain until it had the form of a cylinder about 30μ long. The movements now took on an entirely different character. The cylinder swelled out at one end, and the swelling progressed as a slow wave forward and backward over the length of the cylinder. Simple flowing movements were replaced by an orderly rhythm of waves of shortening.

Let us take another illustration. Some animals of the simple type we are considering get their living as the spider does, by spreading a net. The net has not the geometrical regularity of those which are hung in the hedgerows where they condense the atmospheric water to such delightful patterns, but not the less are they nets spread to catch prey. The threads are actual processes of the body of the animal—the pseudopodia of the zoologist—and each single thread is a cylinder only a few μ in diameter. Such a cylinder considered as a figure of tension must be highly unstable. The tension of the surface probably is small compared with that of water. Certain evidence would fix it about 45 dynes. The maintenance of this thread of semi-fluid material, therefore, either is due to a solidification of its surface or needs continuous expenditure of energy. The matter does not end here however, for the thread is not a simple cylinder of protoplasm. The substance is in movement; the motion of the minute particles floating in it show that there is an outward and an inward stream or flow, and at the face where the two streams meet the frictional stresses produce double refraction.

Consider also the puzzling discriminations exercised by the surface of these simplest cells. When two parts of the same animal come into contact the surfaces soften and the parts fuse, but this does not occur when different individuals touch.

The living cell is, in fact, a machine, capable of carrying out movements, and of complex growth and differentiation of substance. Oxidative processes are the source of its energy, but the oxidation is not direct, as in the burning of a candle. There is a store of energy which is set free in response to a stimulus, and the intake of oxygen occurs only *afterwards*. The oxygen *restores* the potential. A large variety of ferments are present either actually or potentially. They are set free, and can be identified when the cell is broken down and its material dissolved.

Now, living matter contains from 80 to 90 per cent. of water. In any ordinary dead gel or slime with so much water, diffusion would obliterate differences of state so far as simple chemical substances such as salts are concerned. Initial differences in the state of aggregation of the colloid would not so readily disappear owing to the slow rate of diffusion, but if electrolytes were present they would, by their diffusibility and profound influence upon colloid structure, tend to produce a uniformity. Living matter is remarkable in the fact that we have freedom of interchange of matter, otherwise nutrition would fail, combined with the preservation of sources and sinks of energy in a material which is essentially a fluid.

The most fundamental, and to my mind the most puzzling, problem of living matter lies in this contradiction between the functional and chemical complexity of living matter and the apparent simplicity of its structure. Both microscope and ultra-microscope tell us simply that it is a colloidal sol of high but varying viscosity. The material basis of life is apparently much less structural than, for instance, a simple gel such as, *e.g.*, that of azomethine. This is at first sight merely a translucent yellow glass, but the microscope shows it to be a weld of masses, each of independent origin; each of these masses is a weld of smaller masses arranged in an orderly pattern, and these again are built of ultra-microscopic particles.

The questions which I specially wish to discuss are raised most directly by the phenomena of growth. The growth of living matter has been compared to many things—to the growth of a crystal, among others. In the growth of a crystal, molecules of the same nature as those which constitute the crystal are aggregated to a definite formal pattern. In the growth of living matter, extraneous molecules also are ordered to a particular pattern, but the molecules are not the same as those which constitute the growing mass. Growth is part of

a cycle of chemical and physical changes. The case of the crystal is helpful as furnishing an example of the directive influence of a pre-existent molecular pattern. Perhaps it is not generally known that similar directive action is manifested by dead colloids. Many colloids are systems following a path of change whose form is determined by their previous history. The course of the change with time and at constant temperature of the viscosity of, for instance, a solution of gelatine is determined by the temperature at which the solution was made and by the rate of cooling. If, now, this solution is sown with small portions of another system, say with bits of gel, the path of change is altered completely.

We thus have analogies in the world of dead matter for individuality in the characteristic path of change of colloidal systems, and for the directive influence which underlies growth in both crystals and colloids; but a remarkable feature of living matter is the distance over which such directive influence appears to be exerted. The regeneration of cut nerves perhaps best illustrates this.

Let me first premise that the growth of any part of a cell is controlled in some unknown way by the nucleus. When individuals of the single celled type are cut into pieces most of the fragments grow and regenerate the entire animal; but this power of regenerative growth is limited strictly to those fragments which contain a portion of the nucleus.

Consider now a nerve cell and its related nerve fibre. The latter is a process which grows out from the former, and is covered by certain insulating sheaths. The cell body containing the nucleus varies much in size, but we may put it as roughly equal in volume to a sphere of 50μ to 100μ in diameter. The cell process or axon divested of its insulating sheaths is a delicate rod of protoplasm, 5μ to 10μ in diameter, which, in a large animal such as a whale, may be some metres in length. The integrity and the power of growth of the whole of the axon is dependent upon the nucleus. If the nucleus is destroyed the whole structure perishes, and if the nerve fibre is cut that portion of the axon which is still in connection with the nucleus grows, whilst the part cut off disintegrates and dissolves. The nerve fibre, therefore, furnishes us with an example of a system capable of growth only so long as it is united with a portion of matter, which may be some metres distant and to which it is connected only by a cylinder a few μ in diameter. I do not think that there can be any transport

of actual nutritive material by such a tenuous connecting link. The relation may be a static one, the molecular pattern of the nerve fibre being unstable when isolated from the nerve cell. But such scanty evidence as is available tends to show that it is a dynamic one in the sense that the integrity of the molecular structure of the entire axon is maintained by expenditure of energy. The nucleus and cell body, in upholding the molecular pattern, may be said to exert a directive influence along the whole length of the nerve fibre.

The immediate environment of the growing face of a cut nerve fibre also exerts a remarkable directive influence upon its growth. It must be known to all of you that the severed ends of a nerve will heal so as to give complete restoration of function. The nerve in question may be a bundle of some thousand fibres, along which the nervous impulses which produce the exactly controlled movements of skilled action are transmitted, and the restoration of complete function after section is like the joining together of a bundle of cut telephone wires in such a way as to restore all the connections.

For complete restoration of function it is not necessary to fit the cut ends of the nerves closely together. They may be left in the wound separated by a space of some centimetres. Imagine them so separated. From the central end—that is to say the one whose fibres are still connected with the nerve cells—the axons grow out. The axons of the peripheral end break up and dissolve. Now the growth of the axons is at first aimless in direction, the filaments making their way along lines of least resistance in the spaces of the tissues. After a time, however, they come under some influence emanating from the other cut end of the nerve. They turn and grow as directly as possible towards it, and finally invade the empty sheathes and grow down them. What is the nature of the directive influence? It is without doubt chemical. Some substance diffusing out determines the direction of growth, for when two tiny tubes of celloidin are placed near the cut end, one filled with an emulsion of liver and the other with an emulsion of nerve, the axon filaments grow towards the latter. They are, as it were, attracted by it.

The direction of growth must be determined by the density of a diffusion column. If we take the end of a single axon as the end of a cylinder 5μ in diameter, and if it is inclined at a small angle to the axis of diffusion, the difference in the rate

of growth of different parts of the cylinder needed to orient it must be produced by differences in the concentration of the diffusing substances which occur in distances less than 1μ , measured along the axis of diffusion. I need not emphasise how minute these differences must be.

It looks as though we might have to claim for the axon the perfect sense of direction ascribed by a student to *amoeba*. Asked to describe the response of this animal to an electric current, he said: "When subjected to electricity an *amoeba* withdraws all its pseudopodia except one, and then directs itself to the North Pole!"

Let us consider the directive influence which underlies growth from another point of view. The complex organisation of the higher animals exhibits well-marked periods of growth, decay and death, and the duration of these periods is characteristic of each species—the three score years and ten of man, for instance. But these periods are not obvious in the history of single-cell types, in which the whole cell simply divides to form a new generation. Indeed, the question arises whether decay and death are intrinsic properties of these animals. Individuals of the species *Paramoecium* have been isolated under normal and healthy conditions. Each individual was the starting point of a series of generations, there being on the average two generations in three days, and the rate of division was recorded, the records furnishing the basis for a curve of vitality. Such a curve shows fluctuations of a fairly regular character—"rhythms," they have been called. The curve alternately rises and falls, and each complete rhythm, a rise and a fall that is, lasts about a month. The curve as a whole, however, was found steadily to fall, until at about the hundred-and-seventieth generation the race dies out. This was held to establish the appearance of senile decay in strains isolated from mixture with other strains but otherwise in completely healthy surroundings. The discovery that unfertilised eggs of sea-urchins could be made to develop by immersing them for a few hours in more concentrated sea water suggested the possibility that senility could be cured in protozoa. Therefore, when the period of decay had arrived, and individuals were dying off rapidly, the effect of placing the individuals in various infusions was tried. The infusions of animal tissues were found to give the required result. After exposure to them for a short time the rate of growth and of reproduction reached the normal level, death ceased, and a

strain was maintained in full vigour for 860 generations. The living matter of these cells seems to be potentially immortal.

The point of immediate interest in these experiments is that, in the periods of depressed vitality, the power of heredity in determining form becomes imperfect, and many "monsters" are produced. We have here, then, a wearing out of the directive influence which underlies growth.

In the process of artificial rejuvenescence it cannot be a chemical insufficiency which is made good; it must be a physical state which is restored. This is obvious when we consider a special case. Thirty minutes' immersion of an individual paramecium in 0.1 per cent. potassium phosphate was found to restore vitality, and the effect persisted for 282 generations. The effect cannot be due to the presence in individuals of a trace of the salt, for each generation would halve the amount, so that as early as the twentieth generation less than a millionth part would be left for each individual.

It will be remembered that when a solid surface has been washed by a salt solution the contact potential of the surface with pure water is altered, and, according to Perrin, simple washing with water fails to restore the original state. It is, I expect, the wearing out of this kind of state which leads to senility.

Recent work on nutrition suggests reconsideration of these experiments on protozoa. A diet must, of course, contain water and a supply of fuel in the shape of proteins, fats and carbohydrates. It must also contain substances which do not contribute energy, such as simple salts and a class of substances whose presence has only been recently detected called *vitamines*. Nothing is known of the chemical nature of these substances nor how they act, but incredibly minute quantities are sufficient.

The existence of and need for *vitamines* first appeared, I believe, in connection with the disease *beriberi*. This is a disease of the nerves, and it was noticed that birds fed on polished rice—that is to say, upon rice free from its pericarp—developed *beriberi*, but recovered if the polishings themselves, or an alcoholic extract of the polishings, was added to the white rice.

Once attention was drawn to these accessory foodstuffs instances of their occurrence multiplied quickly. They have been found necessary for mammals, birds and minute plants. Scurvy seems to be due to their absence from preserved foods.

Their influence would appear to be limited to the processes underlying growth. The following two cases illustrate this and also indicate the minute quantities necessary. When young rats are fed upon artificial milk made by mixing together in the right proportions the component substances of ordinary milk, previously separated and purified, they lose weight and die. Now, to convert artificial milk into a perfectly adequate foodstuff all that is needed is the addition of 2 per cent. of ordinary milk. Certain Continental workers challenged this result, but later they had to confess their error, which arose in an interesting way. The commercial pure lactose which they had used to make the artificial milk was found to contain vitamins. Even after four re-crystallisations two grams a day carried enough vitamins for a 50 gram rat. Only by many re-crystallisations is vitamin free lactose produced.

Another case. The common brown diatom of the sea littoral will not grow at all in artificial sea water, but will grow very freely in such water to which as little as 0.2 per cent. of natural sea water has been added.

The intimate connection between vitamins and growth is illustrated by the case of cancerous tumours. Mice can be kept at constant weight on a diet of purified wheat protein, starch, lard, lactose, salts and water. Some mice, previously inoculated with a rapidly growing sarcoma, were put on the artificial diet, others similarly inoculated upon a normal diet of bread and corn. The cancer was found to grow much more slowly in those on the artificial diet. To give an example, a mouse after 52 days of artificial diet showed a tumour only 4 mm. in diameter. It was then put upon normal diet, with the result that in 30 days the tumour was nearly as large as the mouse itself. Too much must not be based upon this result, interesting as it undoubtedly is, until it is fully confirmed.

It has been suggested that vitamins intervene in growth by contributing to the fixation of the molecular pattern of the newly formed substance. Their action has been compared to that, say, of a dextrorotary crystal which by its presence causes a mass of fluid indefinitely larger than itself to deposit right-handed crystals. The analogy can at the best be but rough. The influence of a crystal is limited to directing the system along alternative paths of change, all of which increase the entropy. In the growth of living matter, however, the local change, at any rate, is from simple to complex, from a lower to a higher content of free energy.

The nerve fibre of an adult animal grows only when it is cut. The faculty is latent in the completely functional structures; therefore, though growth and function affect each other, they must be distinct process in the sense that the whole cycle of change of energy and matter which constitutes function may occur without growth. If vitamins intervene in growth by a stereochemical effect upon the construction of new matter, the other class of accessory foodstuffs—namely, the simple salts—stand in interesting contrast, since they exert a directive influence chiefly upon the changes of energy which constitute function. The amplitude, period and form of the contraction wave of the heart are, for instance determined by the nature of the electrolytes present. The rhythm of the heart muscle appears to be based upon the antagonistic action of univalent and bivalent cations. The voluntary muscles have no intrinsic power of rhythmic movement. They respond only to the nervous impulse or to some external stimulus. But one of these muscles immersed in a bath of the right kind and concentration of electrolytes, will beat as regularly as the heart itself. The regulation of respiration—that is to say, the adjustment of the rate and depth of breathing to the needs of the body—also is based upon the extreme sensitiveness of a portion of the brain to variations in the hydrogen-ions concentration in the blood. Normally this has the value $10^{-7.3}$. Scrambling up a mountain 1,000 ft. ascent in 30 minutes alters this only to $10^{-7.1}$.

The physical basis of this hold which electrolytes have on the activities of living matter is clear. The configuration of a colloid is determined as much by the electrolytes present as by its own chemical nature. The inertia of a colloid—that is to say, the degree of resistance it offers to change—is determined by electrolytes, since they provide what Helmholtz calls the “first condition of electrical distribution,” as between the colloid particles. It is possible by eliminating electrolytes to raise the sensitiveness of some colloidal solutions to the point at which they are stable in quartz vessels, but are at once precipitated when transferred to clean glass vessels.

Exposure to distilled water also increases the sensitiveness of the surface of some living cells without destroying it. They will live and thrive in pure distilled water, but a trace of metallic impurity (estimated at 1 in 70,000,000) will quickly destroy them.

Here, I think, a certain broad conclusion is forced upon us. Since electrolytes control the configuration of colloidal systems in respect to the size, number and distribution of the colloid particles, and also shape the path of change of energy in living matter, we may infer that the functional processes of a cell are conditioned by the configuration of the colloid in the sense mentioned above.

The material which manifests the phenomena of life is, as I have said before, nothing more than an optically homogeneous fluid medium, in which are suspended particles. When the store of potential energy is being drawn upon—that is to say, in the functional state of activity—the fluidity is decreased and a transitory stage of gelation may occur. Thus, when the cell substance contracts under stimulation, and in the death change when the potential energy is dissipated as heat fluidity decreases to the point at which Brownian movement of the particles is suppressed.

Also the establishment of the field of force which brings about division of cells in the process of multiplication is accompanied by a local gelation.

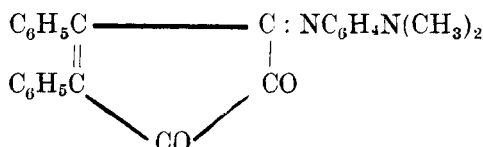
What physical significance can be attached to this decrease in fluidity? According to the theories of Einstein and Hatschek a decrease in the fluidity is due to an increase in the volume of the colloid particles following upon an intake of water from the continuous medium. I do not think so simple a theory covers the facts. Their formula fails except in the case of the simplest hydrosols and suspensions. Actual observation of the process of gelation under the microscope reveals only an inconsiderable change in volume. The main events seem to be, firstly, a damping down of the Brownian movements; and, secondly, an agglutination of the particles into rows which form the fibres of a quasi-rigid framework.

It is practically certain that the process does not go so far as this in normal functional states. The colloid particles maintain their independence, but their relation to each other and to the continuous medium are changed in such a way as to make their potential energy a function of their position. The molecular mechanism of these changes is quite obscure. We may picture to ourselves the colloid particles as strain centres—the microscope justifies so much—and the continuous medium as having the mechanical properties of an unannealed glass. Mechanically a living cell has many points of similarity to a Rupert's drop; indeed, many forms violently disrupt if the

surface "skin" is cut through. Unfortunately we do not know the basis of the simple rigidity of glasses. The absence of any discontinuity in the change from fluid to glass similar to the discontinuity of energy and property which marks the change from fluid to crystal shows that a-glass is a fluid which has lost its characteristic property of fluidity, but to the question why the molecules lose their freedom of movement there is at present absolutely no answer.

One fact may be seized upon—namely, that a change from fluid to a solid of the gel or glass type may be due to quite a small local change in a complex molecule.

Consider, for instance, the substance azomethine, which has the formula :—



This substance has the property of forming rigid gels with *any* solvent; with ether, alcohol, benzene, chloroform, &c. But these very exceptional colloidal properties totally disappear if one hydrogen atom of the side chain is replaced by bromine. I think we are here in a region of molecular physics which is practically unexplored.

The damping of Brownian movements in the course of the functional activity of living matter is, I think, a clue of the first importance to the mechanics of the cell. It suggests a much more extended "grip" of the colloid particle upon the continuous medium than would be indicated by current conceptions of the range of molecular action.

There are properties of simple hydrosols and of suspensions of living cells which point in the same direction. The simplest hydrosols, for instance, seem to have saturation points; that is to say, the number of colloid particles in a cubic millimetre cannot be increased beyond a certain point without occasioning precipitation, and the saturation point seems to be reached when the particles are still widely separated. A similar relation appears in a much more complex system—namely, a suspension of bacteria in a nutritive medium. As the bacteria grow and divide, the rate of growth slackens and finally ceases, but this is not due to exhaustion of the medium, for if the bacteria are filtered or centrifuged off, and the material freshly inoculated, a fresh and copious growth results.

Very little is known about these curious saturation points, but I think you will agree that what is known suggests a range of influence of one particle upon another much greater than the range ascribed to molecular action. Something of the same kind is seen in thin sheets of fluid. A layer of carbon tetrachloride on water exhibits curious mechanical instabilities even when it is of the order of a millimetre in thickness. Such a sheet of liquid is like an unannealed colloid. The tension of the upper face, the air face, is 24 dynes, whilst that of the water face is 50 dynes, and I think there is much to be said in favour of the view that these unequal stresses make themselves felt throughout the entire thickness of the sheet.

I am inclined to suggest the phrase "range of molecular action" must be held to refer to two distinct things—the one is the range of an isolated molecule, say, a molecule of a gas in its free path; the other is the orienting influence of molecules upon one another in the close packed states of fluid, glass, or gel.

The true range of molecular action is that of the gas molecule. It is probably very small, of the order of 10^{-8} cm. But in the close packed states it is probable that the asymmetrical field of force at an interface produces distortion of the external fields of the molecules and orientation extending on either side until it is upset by the heat motion. On this view the transition layer at an interface is a region of more or less fixed molecular pattern, akin, perhaps, to that of a glass. Before the war I had begun to observe particles of interfaces under the ultramicroscope with the object of detecting signs of such structure. It is certain that the Brownian movements are sometimes damped in a remarkable way in this region. The depth of these transition layers might be expected to be increased when the molecules involved are large, or, if small, when the external field of each molecule is markedly asymmetric about the centre of mass. It is significant that the influence of electrolytes upon living matter and upon complex organic colloids with large chemical molecules such as proteins, is determined by the volume of the ion as well as by the charge

* The evidence however is not wholly one-sided. In Einstein and Hatschek's formula for the viscosity of two-phase systems the viscosity is given as a simple fraction of the ratio between the volume of the dispersed phase and the total volume. When the degree of dispersion is high so that the particles of the one phase are ultramicroscopic the viscosity is greater than would be given by the formula. If, now, it is assumed that the discrepancy is due to the volume of the dispersed phase being increased by what might be called adsorption envelopes, it is found that these latter need be only 0.87μ in thickness. But the formula also fails in other respects.

carried; whereas the effect upon simple interfaces between fluid and solid and upon simple suspensions and hydrosols is determined solely by the charge.

Mere increase in size of the molecule must of itself introduce new considerations into molecular physics. The molecular weight of the red pigment of blood, itself a complex protein, is about 16,000; its volume would be equal to some hundred water molecules. The energy related to it when in solution will be its own kinetic energy, and the surface energy of the water molecules surrounding it. Also if it is to be regarded as an elastic structure there will be potential energy due to bulk compression produced by the intrinsic pressure of the fluid.

We are compelled, I think, to attribute surface energy to these large molecules, not, of course, strictly to the molecule itself, but to the displaced water, by the fact that they are aggregated by minute traces of electrolytes in a way resembling the effect upon coarse colloid systems and suspensions. A molecular solution of hæmoglobin is possible only in very pure water.

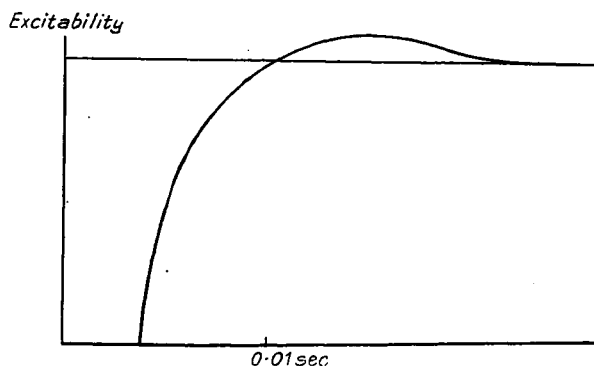
It is curious that large molecules sometimes exhibit simple physical relations. Most proteins obstinately refuse to form states simpler than complex solutions or complex slimes or gels. Some, and hæmoglobin is one of these, readily crystallise. Now hæmoglobin when it crystallises preserves its peculiar optical characters unaltered. It has the same colours and the same absorption bands. It also continues to manifest the same special relations to gases as it has when in solution. Essentially it is unchanged. This continuity of physical properties exhibited by so large a molecule is, I think, startling when considered in relation to Prof. Bragg's account of the structure of crystals.

I have no time to deal with the changes of energy in living matter. The subject is too complex for brief treatment, but I should like to offer a special problem. In general the energy changes of the living cell manifest the ordinary features; they are, for instance, accompanied by the dissipation of a fraction of the energy on heat. One case, however, presents puzzling features—that of the nervous impulse. This is a short wave of molecular change which progresses along the axon filament at about 30 metres a second. It can be started by a local chemical, electrical, or mechanical change. The passage of the wave over any region is followed by a brief period of com-

plete inexcitability, followed by rapid recovery of function. The molecular change involved in the wave is, therefore, one which needs a finite, though very short, time to be recovered from. One would conclude that the wave is a discharge of energy which has to be made good before another discharge can take place.

This conclusion is borne out by the fact that recovery of function can occur only in presence of oxygen, and also by the fact that if the wave passes through a region in which its amplitude is diminished by cold or narcotics it is restored to its full extent so soon as it emerges into a normal region.

The wave would, therefore, appear to be one of chemical change, but if this be so it is one of exceptional character. The temperature coefficient is very low for a chemical change, being



CURVE SHOWING RECOVERY OF EXCITABILITY IN A NERVE AFTER ACTIVITY.

only 1.78 per 10 deg., and there appears to be absolutely no concomitant liberation of heat. The absence of any heat change is, however, I suppose, no more remarkable than the limitation of the rays emitted by phosphorescent animals to visual rays, and the energy of these rays is certainly due to oxidation.

The profound difference between living matter and a simple gel is seen in the selective permeability of the former. Selective absorption of dyes is a common property of gels. Thus, gelatine gels condense basic dyes more than acid dyes. Gels of agar condense acid dyes more than basic dyes. But the permeability of living matter is both curiously selective and variable. The act of fertilisation of the ovum—the entry of the spermatozoon, that is—is followed by a passing rise in

the permeability of the surface. In some cases permeability is said to be unidirectional. When the living skin of the frog is used as an osmometer membrane it is said to permit the passage of carbonic acid in only one direction—namely, from its internal to its external surface. Permeability has been most completely studied in the kidney, and it appears that selective permeability is controlled by or due to an expenditure of energy by the living membranes of the kidney tubules.

The business of the kidney is to maintain the blood of a certain normal composition as regards certain constituents. For our purpose we may regard the blood as a solution of certain colloids—mainly proteins—and of other solutes of simpler molecular character such as urea and salts. The kidney also appears to be chiefly responsible for maintaining the proper reaction of the blood—that is to say, the normal ratio of hydrogen and hydroxyl ions.

Consider first the removal of excess water. This is governed by simple considerations of osmotic and hydrostatic pressure. Incidentally we get clear evidence, if physicists were in need of it, that large molecules, such as those of proteins, exert osmotic pressure. In an osmometer whose membrane is freely permeable by salts, sugar, urea, &c., the blood shows a permanent osmotic pressure of about 35 mm. of mercury. This is the osmotic pressure of what we will call for short the colloids of the blood. It is a critical pressure as regards the elimination of water, for when the blood pressure in the renal arteries falls to about this level the flow of urine ceases, because the hydrostatic pressure of the blood is then equal to the opposing osmotic pressure.

Now there is a certain solution of salts called Ringer's fluid, much in use in biological investigations, which represents very closely the salts of the normal fluids of the body. If some of this solution be injected into the blood there is an immediate flow of urine which is just the Ringer's fluid, or its osmotic equivalent, which has been added. The cause of the flow is obvious. The added Ringer dilutes the blood colloids and lowers the osmotic pressure. The result is that the balance between osmotic pressure and the hydrostatic pressure of the blood is upset and fluid flows out.

That the kidney plays a passive part is proved by the fact that in such a case a copious flow of urine occurs without any increase in the rate of oxidation in the organ. There is thus no expenditure of energy in the process.

That the colloids of the blood plasma exert their influence simply in virtue of their osmotic pressure, and not because of their chemical nature, is proved by the fact that if gelatine be added to the Ringer's fluid in quantity sufficient to give the osmotic pressure of the blood colloids and the fluid injected there is no diuresis. But if soluble starch be added until the viscosity of the Ringer's fluid is, say, twice that of blood (3 per cent. starch), the diuresis is much the same as with simple Ringer's fluid. This is because starch does not sensibly increase the osmotic pressure of Ringer's fluid.

But a flow of urine may be provoked by the injection of alkaloids or of urea or of a simple salt such as sodium sulphate. Consider the case of sodium sulphate. The injection of this salt essentially alters the chemical character of the blood. A diuresis is at once set up and a urine rich in sodium sulphate eliminated. In this case the living membrane discriminates in a remarkable way between sodium sulphate and the normal salts of the blood. That is the usual way in which the physiologist puts it, but it is as well to remember that the discrimination may be due to the remarkable colloid complex which is present in blood plasma. At any rate, be that as it may, a differential treatment is accorded to the sodium sulphate or to, for instance, urea. Such selective diuresis is accomplished only at the expenditure of energy, as appears from the increased intake of oxygen by the organ. The physical processes underlying the transference of solutes or water in the body are probably very complex. For simple transference of fluid through a membrane one's mind turns at once to electric endosmose. When a current is passed through a rod of gel there is an endosmotic movement of water, due to the fact that the colloid particles are usually at a different potential to the fluid bathing them. We may conjecture, therefore, that an electrostatic field maintained across a living membrane would cause transference of fluid. When an expenditure of energy takes place in living matter its potential rises above that of the neighbouring inactive medium. For instance, the contracting portion of a muscle fibre, or the part of a nerve fibre actually conveying a nervous impulse, show a raised potential. Also, when a flow of saliva is excited, the electrical potential of the gland as a whole is altered. There can, therefore, be no question of the ability of a living membrane to produce a difference of potential between its two faces. But in simple electric endosmose the transport of fluid is due to an external field

acting upon that portion of the fluid which is charged, owing to contact with the containing walls. In the living gland there is nothing to take the place of this external field. If a difference of potential is established between the two sides of the living membrane, it is due to a change in the colloid walls themselves.

Suppose a gradient of contact potential were maintained along the length of a tube holding fluid, would a flow of fluid result? I am inclined to think it would, the necessary flux of electricity taking place through the fluid or through the walls.

The transference of fluid in a living cell, instead of being a simple endosmotic phenomenon, is most probably based upon variations in the water-holding power of colloid systems in different states. The imbibition of fluid by a body such as gelatine is a very obscure phenomenon partaking of the character of solution and of endosmotic movement. Whatever its origin, the water-holding power is easily altered. Exposure to the vapour of formaline will completely change the character of the gel. Its structure changes, the gelatine is altered so that it ceases to be soluble in water, and, though there is no immediate change in volume, the gel which has been "coagulated" by the formaline has its vapour pressure raised. It holds water much less firmly. The partial coagulation which occurs in some processes of life, the change from a slime to a rigid gel, for instance, are unquestionably accompanied by variations in the potential, in Gibb's sense, of the water. If the surface film of a colloid membrane separating two masses of fluid were to change in such a way as to lower the potential of the water in it, water would enter the region from both sides simply. But if the change of state were to be propagated as a wave of change starting at one face and dying out at the other face, water would be carried along from the one side of the membrane to the other. A succession of such waves would maintain a flow of fluid.

I should like, in conclusion, to say a word as to the physical knowledge which the biologist is now in need of. The biologist has to deal with the molecular mechanics of gels and slimes. When the formation of a gel is followed by the microscope or the ultra-microscope, the change of state is seen to be due to an increase in size of the colloid particles, followed by their coalescence to form the fibres of a sponge. The fibres of the sponge, in many cases at any rate, are amorphous solids, like a

glass. Now we know that there is no break between the state of fluid and that of glass or gel such as there is between fluid and crystal. Even viscosity shows no discontinuity. Generally speaking, all physical properties pass over without interruption from the one state to the other. A gel or a glass, therefore, is in this sense a fluid which has lost the characteristic property of fluidity. What the biologist first of all wants to know, then, is the molecular mechanism of this change. When a fluid becomes a glass the fields of force about the molecules, as I picture it, become interlocked, so that, although the crystal state is not reached, the potential energy of a molecule in the interior of the mass ceases to be independent of its position. Osborne Reynold's work upon dilatation is helpful in this connection, but I do not think it carries us far.

To understand the gel or slime it is first necessary to understand the fluid state, and, unfortunately, though physics has much to say of the molecular structure of gases and crystals, that of fluids is still very obscure.

Colloidal systems frequently are systems undergoing spontaneous change. As Graham said, they contain "inergia." But in a dead colloid the "inergia" is due to differences of concentration which right themselves slowly owing to the slow rate of diffusion of the solute and to delays caused by internal surfaces. The remarkable hysteresis of surface films similarly springs from the slowness of tangential diffusion, as Gibbs pointed out. The available energy of a dead colloid or of an interface is in the main physical in character. That of living matter is essentially a chemical potential, and the chemical potential gives way in the response to a stimulus, and is restored by an intake of oxygen. The activities of a living cell appear to be due to a cunning combination of the chemistry of the dead space with the hysteresis of the colloid. The well-known drop of mercury in a very dilute acid solution of a chromate might perhaps be taken as a model. The drop is thrown into regular pulsation by intermittent contact with a wire. But the drop of mercury must be reduced in size until the chemistry of its surface becomes a rapidly varying function of its radius, such that if a displacement occurs a train of pulsations results.

ABSTRACT.

The lecture dealt with the physical aspect of some of the phenomena of living matter. At the outset some of the snares and pitfalls which beset the path of the physiologist in search of physical

facts were indicated. One of these was the effect of instinct or intelligence in anticipating altered circumstances, and in setting the appropriate physiological process in action even before the actual change in circumstance had taken place. For example, in some experiments to determine the time lag of increased respiration, it was found that the subject—a cyclist—always anticipated the application of the load and the acceleration of his breathing commenced *before* the actual increase in effort of which it should be the consequence. Then, again, many of the long-accepted theories of the structure of living organisms were ultimately found to be due wholly to the method of killing the organism and preparing it for examination. Exactly similar structures could be obtained in pieces of gelatine if treated in the same way.

Many phenomena were quoted to illustrate the close analogy of many of the functions of living matter to processes familiar to the physicist and physico-chemist. In some of these—for example, the digestive processes of certain organisms—the analogy was so complete that the whole process could be reproduced exactly with non-living material.

The principles underlying growth and development were outlined, and it was shown that growth depended on the presence in the food of *vitamines*. Thus, in the case of white mice fed on artificial milk made by mixing together the purified constituents of ordinary milk, but containing no *vitamines*, growth ceased altogether, while if 2 per cent. of ordinary milk were added to the artificial milk the growth rapidly became normal. Another example of the influence of these *vitamines* was that, in pure distilled water, it was impossible to obtain a development of living organisms, but if the slightest trace of tap water were added—putting a stopper in the bottle which had previously been in a bottle of tap water was sufficient—the organisms would thrive quite normally. The fact that such small proportions of nutriment containing *vitamines* was sufficient suggested a parallel between their action and that of a few crystals thrown into a supersaturated solution of a salt in initiating a crystallisation of the whole.

A further example of the subtle influence of physical laws in physiological phenomena was contained in the explanation of the joining up of severed nerve processes. The directive action involved in this was stated to depend on extremely minute concentration gradients.

Many other interesting phenomena were described and explained.