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A Physicist Looks at Biology

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A mature physicist, acquainting himself for the first time with the problems of biology, is puzzled by the circumstance that there are no "absolute phenomena" in biology. Everything is time bound and space bound. The animal or plant or micro-organism he is working with is but a link in an evolutionary chain of changing forms, none of which has any permanent validity. Even the molecular species and the chemical reactions which he encounters are the fashions of today to be replaced by others as evolution goes on. The organism he is working with is not a particular expression of an ideal organism, but one thread in the infinite web of all living forms, all interrelated and all interdependent. The physicist has been reared in a different atmosphere. The materials and the phenomena he works with are the same here and now as they were at all times and as they are on the most distant stars. He deals with accurately measured quantities and their causal interrelations and in terms of sophisticated conceptual schemes. The outstanding feature of the history of his science is unification: two seemingly separate areas of experience are revealed, from a deeper point of view, to be two different aspects of one and the same thing. Thus, terrestrial and celestial mechanics, for thousands of years totally separate sciences, were reduced to one science by Newton, at a price, it is true - that of introducing the abstract notion of force acting at a distance and the notions of calculus. Thus, also, thermodynamics and mechanics were shown to be one and the same thing through the discovery of statistical mechanics, as were chemistry and electricity through the discovery of the proportionality between charge transport and mass transport in electrolysis, at a price - that of introducing atomicity into the concept of electric charge. Thus, optics and electromagnetism turned out to be two aspects of one theory, Maxwell's theory of the electro-magnetic field, at the price of introducing further abstract concepts, those of the field vectors. Thus, above all, chemistry and atomic physics were unified through the conceptual scheme of quantum mechanics, at the highest price of all -that of renouncing the ideal of a causal description in space and time.

The history of biology records discoveries of great generality, like those of the occurrence of sexual reproduction in all living forms, of the cellular structure of organisms, of the ubiquitous presence of closely similar oxidative mechanisms, and many others of lesser generality. It records one great unifying theory, bringing together separate fields: the theory of evolution. To a physicist this is a strange kind of theory. It states, in the first place, that all living forms are interrelated by common descent. This statement is not one that is proved by decisive experiments but one that has become more and more inescapable through centuries of accumulated evidence. At the same time, it is the principle which serves to bring to order vast masses of descriptive taxonomy and geographical distribution. The theory states, further, that evolution has progressed through natural selection of the fittest and the most prolific. The assumption here involved is not whether or not selection occurs. On the contrary, in this respect the theory is tautological, since the organisms best fitted are defined as those which are selected. Rather, the assumption here involved is that the things selected for carry genetic permanence. At the time the theory was proposed this assumption was not proved, in fact in Darwin's time it could not even be stated in clear terms. It gave rise to the basic questions of the new science of genetics : how does heritable variability originate and how is it transmitted ? Eventually it gave rise to the new abstractions: genotype and gene. It is most remarkable how late and how slowly these abstractions were established. Actually,

today the tendency is,to say "genes are just molecules, or hereditary particles," and thus to do away with the abstractions. This, as we shall endeavor to show later on, may be an overstatement of the legitimate claim of molecular physics. On the whole, the successful theories of biology always.have been and are still today simple and concrete. Presumably this is not accidental, but is bound up with the fact that every biological phenomenon is essentially an historical one, one unique situation in the infinite total complex of life.

Such a situation from the outset diminishes the hope of understanding any one living thing by itself and the hope of discovering universal laws, the pride and ambition of physicists. The curiosity remains, though, to grasp more clearly how the same matter, which in physics and in chemistry displays orderly and reproducible and relatively simple properties, arranges itself in the most astounding fashions as soon as it is drawn into the orbit of the living organism. The closer one looks at these performances of matter in living organisms the more impressive the show becomes. The meanest living cell becomes a magic puzzle box full of elaborate and changing molecules, and far outstrips all chemical laboratories of man in the skill of organic synthesis performed with ease, expedition, and good judgment of balance. The complex accomplishment of any one living cell is part and parcel of the first-mentioned feature, that any one cell represents more an historical than a physical event. These complex things do not rise every day by spontaneous generation from the nonliving matter - if they did, they would really be reproducible and timeless phenomena, comparable to the crystalization of a solution, and would belong to the subject matter of physics proper. No, any living cell carries with it the experiences of a billion years of experimentation by its ancestors. You cannot expect to explain so wise an old bird in a few simple words.

Perhaps one can hope to understand some of its features - how oxygen is transported, how food is digested, how muscles contract, how nerves conduct, how the senses perceive, etc. One hopes to fix one's attention on features of the greatest generality, features that are an expression of the organization of matter as it is peculiar to all living matter, and to living matter only, to living protoplasm. Do such features really exist ? Take, for example, the so-called excitability of living cells. Textbooks of physiology assure us that excitability is a peculiarity of all living cells. From a physicist's point of view this feature may perhaps best be expressed in the following terms: a living cell is a system in flux equilibrium, matter and energy are taken in from the environment, are metabolized and partly assimilated, partly degenerated, and waste products are given back to the environment. To a first approximation, that in which growth is neglected, this represents a steady state. As long as the environment does not change, the cell does not change even though matter and energy flow through it. If the environment does change slowly, the state of the cell will also change slowly and continuously, but if the environment changes sufficiently rapidly the state of the cell will change abruptly. It will become excited. Thus, upon excitation a nerve cell will discharge an action current, a muscle fiber will contract, a sensory cell will discharge, and similarly all other kinds of cells under proper conditions of stimulation will produce a disproportionately large response to a relatively slight but rapid change in the environment. Do we here deal with a truly general feature of the organization of matter in living cells ? More than a hundred years ago Weber went one step further and formulated quantitatively a general law relating the threshold of stimulation with the parameters characterizing the environment. The law can be most easily formulated for situations in which one external parameter, say, the light intensity, changes abruptly from one level to another. Weber's law then states that the threshold change of this parameter which will produce excitation is proportional to the initial value of the parameter. For instance, if at an illumination of 100 foot candles, a change of 5 foot candles to 105 foot candles is necessary to produce excitation, then at a 10 times greater intensity of illumination of 1000 foot candles, a ten times greater change of 50 foot candles to 1050 foot candles will be necessary to cause excitation. The rating which this law of Weber has received in the biological literature has fluctuated from generation to generation, and has reached a very low level in recent times, so low in fact that it is barely mentioned in many of the current text books of physiology. The reasons for this decline furnish an instructive example of our perplexities regarding biological theory. In the first place it is quite clear that the law as stated experimentally can only be expected to hold over a limited range. It must fail at exceedingly low stimulus levels where the proportionate changes in stimulus fall below the size of individual quanta of action, and it must fail at exceedingly high stimulus levels where secondary effects of the stimulus

become damaging to the cell. Experimentally, therefore, the validity of the law can only be apparent in a middle region of varying extent. In an ordinary physical law such limitations would not detract from its intrinsic value as a structural unit in the general theoretical edifice. Thus Boyle's law relating pressure and density of a gas fails at high density, where the molecules get crowded for space. Yet Boyle's law has been one of the chief clues to the kinetic theory of gases, and thus to atomic theory. A physicist would not be tempted to belittle a law merely because it is valid only over a limited range. Not so in biology. The biologist is tempted to discard the law altogether and say that it is an artefact. The threshold for stimulation, as a function of stimulus, may not really be proportional to the stimulus, with deviations from this law due to secondary causes at very low and at very high stimulus levels, but may be represented by an ill defined curve, running straight for a shorter or longer stretch. In fact, one can explain even a rather extended straight portion of this curve by appealing to the adaptive value that such a shape of the curve might have. It is perhaps reasonable to say that a proportionality of threshold with stimulus represents an advantageous situation for a cell that has to adjust to a very wide range of stimulus level, and thus to make natural selection responsible for simulating something that looks a physical law, natural selection acting like the overly faithful assistant of a credulous professor, the assistant being so anxious to please that he discards all those data which conflict with his master's theory. Arguments of this kind, combined with our total lack of a proper theory of excitation and the fact that perception in higher organisms anyhow is known to be a very complex business, have led to the present decline in the rating of Weber's law. It remains to be seen whether closer quantitative studies of the law, particularly as displayed by the simplest organisms, will justify this low rating, or whether it will turn out that we have overlooked a powerful clue to the nature of the organization ofthe living cell. The situationjust described is one frequently met with in biology.

If it be true that the essence of life is the accumulation of experience through the generations, then one may perhaps suspect that the key problem of biology, from the physicist's point of view, is how living matter manages to record and perpetuate its experiences. Look at a single bacterium in a large volume of fluid of suitable chemical composition. It assimilates substance, grows in length, divides in two. The two daughters do the same, like the broomstick of the Sorcerer's apprentice. Occasionally the replica will be slightly faulty and an individual arises with somewhat different properties, and it perpetuates itself in this modified form. It is quite easy to believe that the game of evolution is on once the trick of reproduction, covariant on mutation, has been discovered, and that the variety of types will be multiplied indefinitely.

Higher organisms manage the matter of reproduction in a slightly more sophisticated manner, insisting on biparental reproduction, giving each new individual something from each parent, namely, one half of what the parent itself received from its parents, the half selected by an elaborate lottery. The student of evolution appreciates this game of segregation and recombination as a clever trick for trying out heredity in new combinations; it is not the basic thing but a refinement and elaboration of the really marvelous accomplishment: ordinary, uni-parental reproduction.

A physicist would like to know how this ordinary reproduction is done. This seems to be the elementary phenomenon of living matter. What sort of a thing is it, from the molecular point of view ? What is the most elementary level upon which it can be observed ? The answer to this question is that the cellular level is the most elementary level. There is a variety of approaches to this question, but none of these leads essentially below the cellular level.

Take for instance, ordinary classical genetics of some higher organism. We find that heredity is controlled by genes linearly arranged in chromosomes, and it might seem that the problem of reproduction has been reduced to that of the reproduction of the genes, but this is not true because no gene has been observed to reproduce except within the intact functional cell. We have every reason to believe that this dependence on the intactness of the cell is an essential one. The fact that there are many different genes in each cell, and that we have learned to combine different sets of genes in hybridization experiments, teaches us that the thing that is reproduced is a complex thing, but does not teach us how to break down the problem into simpler problems. Or, for instance, take the reproduction of a virus particle, that of a bacterial virus. A single virus particle will enter a bacterial cell and twenty minutes later

several hundred virus particles identical with the one which infected the cell may be liberated. At first sight this may seem simpler than cellular reproduction because the individual virus particle is a very much smaller unit than the individual cell and may be analogous to an individual gene or to a small group of genes. In some respects, however, this case is really more complex than that of the reproduction of a cell. In the first place, it, too, requires the presence of a living and functional cell, and in the second place, what is observed is not a reproduction from one to two elements, but from one to several hundred. This feature makes it more complex than an ordinary cell division. Moreover, the complexities of sexual reproduction and of recombination are not eliminated by going to this seemingly elementary level. We have learned recently that when a bacterium is simultaneously infected with two similar but different virus particles, the progeny will contain recombinants in high proportions. From this we draw two conclusions: that the virus particles themselves are complex, and that their reproduction must involve manoeuvers analogous to those occurring in meiosis and conjugation of higher organisms. This is news that is exciting principally by the blow it deals to our fond hope of analyzing a simple situation. Perhaps one might think that it would help to break up the bacterium prematurely, before the end of its natural term. An ingenious technique to do this has actually been developed by Doermann. He finds that up to about half time there are no active virus particles, thereafter they increase rapidly in number up to the end of the natural term. Since no active virus particles are found before half time, although at least one was necessary to initiate virus reproduction in the bacterium, the infecting particles must be greatly modified if not actually broken down into subunits. It seems that the real reproduction and recombination has already occurred during the first dark period when no active particle can be detected, because when the first complete particles appear they contain as high a proportion of recombinants as will be found in the ultimate total crop of a full term liberations Thus, the technique of early inspection did not bring us an essential simplification of the problem.

The hopes associated with the study of bacterial viruses are based on one other feature, the ability to control and vary the experimental conditions under which reproduction occurs, and indeed in this respect we have learned something. We have learned that the reproduction of the virus particles in the bacterial cell requires that the cell be very actively assimilating. In fact, it seems that this is what happens: the virus particle which enters the bacterium commandeers the assimilatory apparatus of the bacterium. The primary products of assimilation, instead of being used to make bacterial substance, are used largely or exclusively to make virus particles of the type that enter. We have no clue whatsoever as to how the virus particle manages to shunt the utilization of assimilatory products into its own channels nor how the reproduction proper is done. Presumably this situation can be analyzed from the biochemical point of view in considerably more detail. Since we know that the virus substance comes largely from assimilates after infection, we could ask more specifically in what order the assimilates acquired are incorporated. In principle this can be done with radio-active tracer experiments by adding or removing.labelled compounds at given times after infection of the bacterium. Moreover, by using bacterial strains unable to synthesize one or another major component of the virus particle, say, an amino acid or a purine, one might hope to analyze the pathway by which these constituents are incorporated into the virus particle. It is however not clear to me how experiments of this kind could give a clue to the key problem, the chemical mechanism of replication.

Another way to approach the problem of reproduction is to center one's attention on some of the cellular constituents outside of the chromosomes which seem to have genetic continuity. To this class belong the plastids of green plants and a number of specific structures in protozoa. Here too, however, the genetic continuity is strictly dependent upon the functioning of the whole cell, and since these bodies can only be identified with assurance if they are large enough to be visible under the microscope they do not offer any simplification of the basic problem. There is reason to suspect that genetic continuity is also involved in the production of the enzymes elaborated by the living cells. If this is so, enzymes may be the best material for the study of this key problem but at present the mechanisms involved in enzyme synthesis are not clearly understood. There seem to be four factors involved in the production of any particular enzymes The first is the external metabolism supplying energy and assimilates. The second is a genetic control of the following kind: one finds that a very specific and limited genetic change, a mutation of a single gene, can be responsible for whether or not a cell can manufacture a given enzyme. A third factor is the substrate upon which this enzyme is supposed to act. In many cases a cell which is

genetically able to produce a certain enzyme and is well supplied with nutrients, will not produce this enzyme except in the presence of the particular substance upon which this enzyme can act. One says that the cell responds adaptively to the presence of the substance. It is even possible that every enzyme requires for its formation the presence of its specific substance, only we do not become aware of this necessity because the substance in question may be present within the cell as a normal intermediary metabolite at all times. This adaptive mechanism is obviously of enormous value to the economy of the cell. The cell can thus shift its limited manufacturing capacity into a great variety of channels according to what is offered by a changing chemical environment. While we can readily understand the usefulness of this mechanism, we do not in the least understand its chemical nature. Is it that any substance merely stabilizes corresponding enzyme molecules that are continuously formed even in its absence but would be quickly destroyed if it were not for the stabilization ? This notion has been urged by several authors, but it is an unlikely one. An enzyme molecule that is stable only as long as it is held in the claws of iistsubstrate would be pretty useless. It would vanish too quickly if the concentration of the substance is reduced below the level at which the enzyme is saturated with it. Arguments of this kind cannot yet be very well evaluated quantitatively because of the intervention of the fourth factor involved in enzyme synthesis. This factor becomes apparent in experiments in which a cell is offered simultaneously two different substances, for each of which it can form adaptive enzymes which differ from each other. It is then found that these two adaptations compete and interfere with each other. This could not happen if the adaptation merely consisted in the stabilization of enzymes. The phenomenon of interference between different adaptations indicates a power on the part of any enzyme forming process to commandeer supplies into its own channel. In other words, the enzyme forming process, too, involves some kind of self accelerating mechanism. As yet, however, we are not able to pin down the element responsible for this power. Is it the enzyme itself, an unspecific precursor, a specific region of the enzyme, or any one of these combined with substrate ? I believe a great deal of light could be shed on this situation by a much closer analysis than has hitherto been attempted of the adaptation interference phenomenon.

I have been trying to give you an impression of the intellectual uncertainties confronting a physicist entering biology. These are of two kinds. On the one hand, when he thinks he has discovered a law of nature as pertaining to living matter, like Weber's law, he must beware lest he be fooled by natural selection simulating such a law. On the other hand, when he has found a really fine phenomenon universal in the living world and specific to it, like reproduction, he finds that it is indissolubly tied into the enormously complex organization of a living cell. Baffled by these barriers to his usual approach, a physicist may well stop and consider what he may reasonably expect by way of theoretical progress in the application of physical principles to living matter. It is true that physics and chemistry have a firm hold over biology by virtue of two great generalizations: living matter is made up of the same elements as those of the inanimate world, and conservation of energy is valid for processes occurring in living matter, just as it is for all processes in the inanimate world. To the men who first established the validity of these generalizations for living matter, like Helmholtz, for instance, it seemed clear that the processes of living matter must be essentially the same as those of the inorganic world and that there could not possibly exist a biological science ruled by its own laws. For these men the phenomena of life presented essentially mechanical problems. They should be deducible from the laws of Newton's mechanics as movements of particles due to forces originating in other particles. Such a view, more recently slightly modified to incorporate a few quantum concepts, has been the driving force of several generations of biochemists. We may quote J. Loeb as fairly representative of this attitude : "The ultimate aim of the physical sciences is the visualization of all phenomena in terms of groupings and displacements of ultimate particles, and since there is no discontinuity between the matter constituting the living and the non-living world the goal of biology can be expressed in the same way." One should add at this point that some of the contemporaries of Newton took quite a different view of the Newtonian principles. To describe motions in terms of forces acting at a distance seemed to them like introducing magic. Moreover, to correlate forces with accelerations, that is, with the second derivative of the function describing the motion, seemed to them the height of abstraction, going beyond what should be permitted to occur in any science, and threatening to remove it from the realm of rational pursuit. Between the times of Newton and Helmholtz, then, a strange inversion took place. What had seemed magical and extravagant at the earlier period, after a century of success had become the only way in which one could hope to account rationally and visualizably for the phenomena of nature. Actually, most branches of

biology manage to flourish without any recourse to this ideal. All of natural history operates with a system of concepts which has very little contact with the physical and chemical sciences. The habits of animals and plants, their reproduction and development, their relations to their symbionts and to their enemies, can all be described and analyzed with very little reference to the concepts of physics and chemistry. Perhaps the most notable of these independent branches of biology is genetics, which in its pure form operates with "hereditary factors" and "phenotypic characters" in a perfectly logical system, as an exact science without ever having to refer to the processes by which the characters originate from the factors: The root of this science lies in the existence of natural units of observation, the individual living organisms, which in genetics play somewhat the same role as the atoms and molecules in chemistry.

This analogy of the individual living organism with the molecules of chemistry may be valid in more than one sense. In the first place the notion of the individual organism brings into biology discreteness, and number, and identity of type, as the concept of molecule does in chemistry. In the second place, the stability and reproducibility of type in biology we think is a result of the stability and reproducibility of the genes and this stability we think is based upon the stability of certain complex molecular structures. The third and perhaps the most interesting aspect of the analogy is the fact that the individual organism presents an indissoluble unit, barring us, at least at present, from a reduction to the terms of molecular physics. It may turn out that this bar is not really an essential one, but a physicist is well prepared to find that it is essential. This would be similar to the lesson the physicist had to learn most recently in the attempts to develop a proper approach to an 'understanding of the properties of molecules in terms of their constituent elements. To make this point clearer I want to illustrate it with an historical example. At the beginning of this century enough was known about the existence of atoms and molecules to make the question of their structure a real one. The analysis of the interaction of atoms with light had begun before the constituent elements of the atoms, electron and nucleus had been discovered. It was known that atoms emit radiations of characteristic frequencies which could be determined with high accuracy. The attitude of the physicists of those days was that these characteristic frequencies represent frequencies of vibration of the atoms themselves and as such are expressions of certain properties of the atoms as mechanical systems. Examples of solid objects having characteristic frequencies of vibration had been well worked out and understood in terms of classical physics. The vibrations of the atoms were presumed to be vibrations of electrical matter within the atoms and it was considered the task of future analysis to infer the structure of the atom from a close inspection of the frequencies of vibration and of the conditions under which atoms could be excited in their various modes of vibration. Nothing could have seemed more sane and reasonable a program of research. In fact, many interesting regularities in the system of frequencies characteristic for a given atom were discovered. As long as nothing definite was known of the parts of which atoms are made up, these findings may have seemed a little strange but by no means suggestive that a suitable description in terms of a mechanical model could not be obtained. The situation was changed suddenly when it became clear that every atom is made up of one nucleus and a number of electrons. Very simple and general arguments could be brought forward showing that no system consisting of these elements could possibly have the properties that atoms were known to have. Here was a clear paradox. In Bohr's paper of 1913 this paradox was met by introducing the notions of stable orbits and jumps between these orbits. The frequencies of revolution of electrons in these orbits were unrelated to the frequencies of the light waves emitted. These were very irrational assumptions which shocked and in fact disgusted many physicists of that time.

The crucial point in this abbreviated account of an historical episode is the appearance of a conflict between separate areas of experience, which gradually sharpens into a paradox and must then be resolved by a radically new approach.

As is well known, the resolution of the paradoxes of atomic structure necessitated a revision of our ideals (or prejudices) regarding the description of nature. It was necessary to replace the classical conceptual scheme of particles moving in well defined orbits by the new scheme of quantum states and transition probabilities. Let us consider, for instance, a hydrogen

atom in an excited state. Quantum mechanics permits us to calculate the probability that the atom will

make a transition to the ground state in a definite time interval, with emission of a light quantum which carries off the difference in energy between the two states. Suppose we wanted to improve the statistical prediction and find out exactly at what moment the transition will take place. To make such a prediction we would need more precise information regarding the state of the atom, beyond the fact that it is in this excited state. We might try to obtain this more precise information by finding out at what point within the atom the electron is located at a certain moment. Such information can be obtained, in principle at least, by using an ideal microscope employing a radiation of very short wave length. Observation with light of such very short wave lengths, however, necessitates the use of an experimental arrangement in which we cannot control the exchange of energy between the atom and the measuring instrument, the light in this case. This uncontrolled exchange of energy will be of such a magnitude that the atom thereafter will be in any one of the excited states. If the first aim, that of obtaining the precise location of the electron, is not to be sacrificed, the microscope has to be used in a fashion which is mutually exclusive with any arrangement designed to give us information about the excited state. While, therefore, obtaining exact information regarding the position of the electron at this particular moment, the uncontrolled interaction between the tool of observation, the short wave light, and the atom introduces an uncertainty in the energy of the atom and we are not better off than before. We have just swapped the knowledge of a stationary state for the knowledge of the location of the electron at one particular moment, and our primary aim of additional information, beyond that of knowing that the atom is in the first excited state, has been frustrated. This state of affairs is at the root of all quantum phenomena. Each process of observation has an individuality which cannot be broken down beyond a certain limit and different types of observation stand to each other in a mutually exclusive, complementary relationship. Different observations will therefore lead to a variety of optimal informations regarding an atomic system, and each such optimal information we describe by the abstract notion of the state of that system. From such knowledge we can make precise statistical predictions regarding the future of the system. The different optimal informations are obtained from mutually exclusive experimental arrangements, and the quantum mechanical formalism is designed to embody this particular feature of complementariness. We believe that quantum mechanics is the final word as regards the behavior of atoms and we base this belief upon the analysis by Bohr and Heisenberg of the possibilities of observation, which shows that the renunciation of the ideal of classical physics for the description of Nature eliminates nothing that could be defined operationally. Therefore this renunciation should not be considered as a loss but as a liberation from unnecessary restrictions and thus as the essential element of our advance which opened the widest possibilities for future developments.

Let us now go back to the situation as it appeared to Helmholtz in the 1870's. For him it seemed that the behavior of living cells should be accountable in terms of motions of molecules acting under certain fixed force laws. How far we have wandered from this ideal ! We now know that if we tried to adhere to this ideal we could not even account for the behavior of a single hydrogen atom. In fact, we account for the stationary state of the hydrogen atom precisely at the price of not describing the motion of the electron. But how about the living cell ? Should we now perhaps consider it as a super molecule and ideally calculate its stationary states and transition probabilities ? Would it be sufficient to modify Helmholtz's views to this slight extent ?

Such a view might seem reasonable to the structural chemist, who applies the general concepts of quantum mechanics successfully to more and more complex molecules. Even though his efforts have not yet been successful with any structures of molecular weight higher than a few thousand, a limitation in principle can hardly be expected. However, the experimental analysis of the structural chemist always presupposes the availability of a practically infinite number of molecules of the same kind, and of a practically infinite stability of the molecules if not disturbed.

In the living cell we know that a great deal depends on very fine features of structure. By structure we mean relevant inhomogeneities in the make-up of the cell. These relevant inhomogeneities go right down to the atomic scale. It would certainly not be possible, even in an ideal experiment, from observation of ari individual living cell to gain knowledge of these details sufficient to make quantum mechanical calculations of the development of the cell. To make structural observations of such extreme finesse again a practically infinite number of cells in identical quantum states would be required. Such a

requirement can certainly not be met in practice and it seems likely to me that also it cannot be met in principle. This leads to the point of the third analogy between individual living organisms and molecules. It may turn out that certain features of the living cell, including perhaps even replication, stand in a mutually exclusive relationship to the strict application of quantum mechanics, and that a new conceptual language has to be developed to embrace this situation. The limitation in the applicability of present day physics may then prove to be, not the dead end of our search, but the open door to the admission of fresh views of the matter. Just as we find features of the atom, its stability, for instance, which are not reducible to mechanics, we may find features of the living cell which are not reducible to atomic physics but whose appearance stands in a complementary relationship to those of atomic physics.

This idea, which is due to Bohr, puts the relation between physics and biology on a new footing. Instead of aiming from the molecular physics end at the whole of the phenomena exhibited by the living cell, we now expect to find natural limits to this approach, and thereby implicitly new virgin territories on which laws may hold which involve new concepts and which are only loosely related to those of physics, by virtue of the fact that they apply to phenomena whose appearance is conditioned on not making observations of the type needed for a consistent interpretation in terms of atomic physics.

I would like to explain this point of view a little further by a brief reference to the problem of spontaneous generation. We know that life originated on earth within less than a billion years after conditions had become reasonable, perhaps in much less time and perhaps not once but repeatedly. We do not know the chemical environment of those days, but it can hardly have been anything that could not be reproduced today nor is it likely to have been anything very specific. Therefore, spontaneous generation should be an experimentally reproducible phenomenon. Imagine that we knew these conditions. We could then prescribe a certain synthetic medium and temperature and predict that spontaneous generation should occur with a certain probability per time unit, and it would seem that this would bring life completely into the domain of chemistry. Or would it ? Conceivably spontaneous generation would be a very gradual thing, going through lengthy stages ofinaccurate and poorly defined replications, perhaps evolving from something like crystallization from supersaturated solutions. In that event the algebra of natural selection and of statistical fluctuations would enter decisively into the kinetics of spontaneous generation and would limit the predictability of the outcome, just as it does in the later stages of evolution. The creatures emerging in such a test tube experiment presumably would be extremely different, biochemically, from those of our world, and not being adapted to our world would have no chance of survival in it. This implies that we could not tell the precise chemical make-up of a living thing from its mode of chemical origin. Nor can we tell it, as pointed out before, from a structural analysis of its actual state. The detailed chemical structure of a living cell is thus operationally undefinable and the concept therefore meaningless. It remains to be seen whether a retrenchment in the demand for a detailed chemical description for such phenomena as replication, chromosome movements, excitation, active transport, etc., will facilitate giving a coherent account of these phenomena.

Perhaps you will think that such speculations and arguments as here presented are very dangerous: they seem to encourage defeatism before it is necessary, and to open the door to wild and unreasonablespeculations of a vitalistic kind. I sympathize with this criticism and want to justify the presentation I have given by saying that Bohr's suggestion of a complementarity situation in biology, analogous to that in physics, has been the prime motive for the interest in biology of at least one physicist and may possibly play a similar role for other physicists who come into the field of biology. Biology is a very interesting field to enter for anyone, by the vastness of its structure and the extraordinary variety of strange facts it has collected, but to the physicist it is also a depressing subject, because, insofar as physical explanations of seemingly physical phenomena go, like excitation, or chromosome movements, or replication, the analysis seems to have stalled around in a semidescriptive manner without noticeably progressing towards a radical physical explanation. He may be told that the only real access of atomic physics to biology is through biochemistry. Listening to the story of modern biochemistry he might become persuaded that the cell is a sack full of enzymes acting on substrates converting them through various intermediate stages either into cell substance or into waste products. The enzymes must be situated in their proper strategic positions to perform their duties in a well regulated fashion. They in turn must be synthesized and must be brought into position by manoeuvers

which are not yet understood, but which, at first sight at least, do not necessarily seem to differ in nature from the rest of biochemistry. Indeed, the vista of the biochemist is one with an infinite horizon. And yet, this program of explaining the simple through the complex smacks suspiciously of the program of explaining atoms in terms of complex mechanical models. It looks sane until the paradoxes crop up and come into sharper focus. In biology we are not yet at the point where we are presented with clear paradoxes and this will not happen until the analysis of the behavior of living cells has been carried into far greater detail. This analysis should be done on the living cell's own terms and the theories should be formulated without fear of contradicting molecular physics. I believe that it is in this direction that physicists will show the greatest zeal and will create a new intellectual approach to biology which would lend meaning to the ill-used term biophysics.

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