THE LIVING STATE

With Observations on Cancer

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PREFACE

It would take a superhuman ability to explore the deeper foundations of life. What one can do, more hopefully, is to investigate just a few of its facets. This booklet is a very personal account of some of my own researches. It is neither complete nor continuous. I have omitted even much of my own work. No mention is made, for instance, of my work on metabolism, the C_4 dicarboxylic acid catalysis which was honored by the Nobel Prize and which has led to the Krebs cycle.

References will be found at the end of each chapter. I have tried to summarize the work of authors who have done extensive research.

In its early phases my research was generously supported by the National Institutes of Health. My thanks are due to all those who have helped to keep me "above water" since, particularly the Josephine B. Crane Foundation. My thanks are also due to the National Science Foundation (Grant GB 29395) and to the L. and L. Foundation. I gratefully acknowledge the assistance of my faithful associates Miss Jane A. McLaughlin and Miss Barbara Perry, and of Dr. L. S. Együd. I also want to thank my friend Dr. John Platt for his painstaking criticism. Last, but not least, I owe a debt of gratitude to the Marine Biological Laboratory, Woods Hole for providing me with a scientific home.

Albert Szent-Györgyi

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I

INTRODUCTION

Every biologist has at some time asked "What is life?" and none has ever given a satisfactory answer. Science is built on the premise that Nature answers intelligent questions intelligently; so if no answer exists, there must be something wrong with the question. Life, as such, does not exist. What we can see and measure are material systems which have the wonderful quality of "being alive." What we can ask more hopefully is "What are the properties which bring matter to life?"

Though I do not know what life is, I have no doubt as to whether my dog is alive or dead. We know life by the existence of things for which there is no direct physical reason and which even seem contrary to the rules of physics. Life appears to be a revolt against the rules of

Nature. It resembles the anarchistic conspiracy of Chesterton (1930) which was aimed at the abolition of all rules, but had rules of its own, stricter than the ones against which it revolted. Life is a paradox. It is easy to understand why man always divided his world into "animate" and "inanimate," *anima* meaning a soul, the presence of which had to explain queer behavior.

The most basic rule of inanimate nature is that it tends toward equilbrium which is at the maximum of entropy and the minimum of free energy. As shown so delightfully by Schrödinger in his little book, "What is Life" (1945), the main characteristic of life is that it tends to decrease its entropy. It also tends to increase its free energy. Maximum entropy means complete randomness, disorder. Life is made possible by order, structure, a pattern, which is the opposite of entropy. This pattern is our chief possession, it was developed over billions of years. The main aim of our individual existence is its conservation and transmission.

Pattern and structure can turn things around. As a rule, opposite charges approach, neutralize one another, and produce motion. Within structures, such as that of a dynamo, it is motion which separates charges. Life took its own course when its first pattern was established. Life is a revolt against the statistical rules of physics. Death means that the revolt subsided and statistical laws resumed their sway.

Trying to approach life we must bear these relations in mind to avoid acting as Tyndall's chemist did, who, when asked to find out what a dynamo was, dissolved it in hydrochloric acid. So when trying to understand life we must bear pattern in mind, the specific relations being summed up by the word "organization" which means that the whole is more than the sum of its parts, $2 + 2 > 4$, which is the basic mathematical equation of biology. When dissolving the system into its parts, we end up with 2's having lost the $>$.

In arranging atoms into molecules, say, protein molecules, Nature passes through three stages of organization. First she produces fibers, a linear array, arranging the atoms relative to one another to achieve the proper "configuration." Then she folds up the fiber to achieve a specific "conformation." Eventually she brings the various molecules into a specific relation relative to one another, establishing "coordination." The molecules, thus ordered, may influence and alter each other's properties and produce reactions even over distances.

When the chemist or physicist wants to study the interaction of two particles, say, two molecules, he tries to isolate them to avoid outside interference. Should he want to transfer, for example, an electron from molecule A to molecule B

$$A + B \rightleftharpoons A^{+} + B^{-}$$

he will probably calculate the energy needed to separate a plus and minus charge, calculate ionization potentials and electron affinities. But life is mostly the result of a series, a chain of reactions, and knowledge of a single reaction has but limited value. So if A and B are members of an electron-transfer chain, A, while transferring an electron to B, may receive a new electron which will abolish its plus charge. So there will be no force to pull the electron back from B, and electrons may smoothly flow through the chain, from A to B, from B to C, etc.

An important difference between pure physics and biophysics is in probability.* While physics is the sci-

*Probability has a deep physical meaning. The most probable state of the universe is that of a minimum of free energy and maximum of entropy, randomness. This is the state toward which ence of the probable, biology is, in a way, the science of the improbable. Probable chemical reactions occur spontaneously. If biological reactions were "probable," they would take place spontaneously, and we would burn up; our machine would run down as a watch relieved of its regulation. Life, on principle, has to work with improbable reactions which it then makes proceed by specific routes, thereby regulating them. Life, altogether, is an improbable phenomenon which was generated, perhaps, but once during the billions of years of the history of

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the universe tends, which makes time flow in its present direction. Once this state is reached, there will be no life. What, then, keeps the universe from reaching this point? This has been discussed by Dyson (1971). Why do not all energy-producing reactions take place, letting the entire biosphere run down? The situation is analogous to that of a rock on the mountain side. A rock rolling down liberates great amounts of energy, and if the mountain does not crumble it is because loosening rocks demand a small amount of energy that has to be invested before the rock can start rolling; this energy is not available. The energy liberated by the rolling rock may be very great compared to the energy which has to be invested, and if there were a way to have the energy, liberated by rolling rocks, used for loosening new rocks, mountains would disappear. What keeps mountains standing is the small amount of initial investment.

Similarly, to make a chemical reaction proceed, as a rule, a relatively small amount of "activation energy" has to be invested. This is what keeps the biosphere from running down. What life does is to decrease the necessary initial investment by means of enzymes, till the small amount of energy supplied by heat agitation becomes sufficient to make the reaction proceed. Life, then, conserves the energy liberated to initiate new reactions. From an energy point of view life rests on three pillars. One is the decrease of activation energy, accomplished by enzymes. The second is the conservation of the energy liberated and its investment in new reactions. This is done by means of the "high energy phosphates," ~P's. The third is photosynthesis, by means of which life uses the radiation energy of the sun to build new molecules from which energy can be liberated.

the world. If I were to ask a physicist what the probability was that the trillions of electrons and atomic nuclei would get together and stay in the relative position they are in me, the answer would be that the probability was practically zero, which means that I am impossible. One of the main aims of biology is to find out the way in which life makes reactions proceed, thereby perfecting itself.

When pursuing this analysis we must be careful not to kid ourselves into believing that we understand, when we do not. Analyzing living systems we often have to pull them to pieces, decompose complex biological happenings into single reactions. The smaller and simpler the system we study, the more it will satisfy the rules of physics and chemistry, the more we will "understand" it, but also the less "alive" it will be. So when we have broken down living systems to molecules and analyzed their behavior we may kid outselves into believing that we know what life is, forgetting that molecules have no life at all.

We must also be very careful of how we ask questions, for by the way we ask them we may determine the answer. If we ask Nature "Is light a particle?" Nature will answer "Yes, it is a particle." But if we ask "Is it a wave?" Nature will answer "It is a wave." Is a gramaphone playing a Bach record a purely physical system? The answer is "Yes it is." The needle follows the groove and the membrane follows the needle. The only thing I left out was the genius of Bach without which the whole thing would make no sense. My watch too, is a purely physical system, but I should not forget the generations of watchmakers who have developed this wonderful little gadget which could never have come together by random fluctuations.

Every action must have its underlying mechanism, and a system can only do what its structure allows it to do. A record player will never write a letter, a typewriter will never make music, and a cow will never be able to lay an egg, however hard she tries. But once the system is there it will be able to do what its structure allows it to do. So structure and function are, in a way, identical, and we may study either or, more correctly, must study both on all levels. They are one. Structure generates function, function generates structure. For thousands of years man has observed living structures on the macroscopic level. For a century man has studied them on the microscopic level. At present we are concentrating on the molecular level, below which the electronic level awaits exploration, the road having been paved by the Pullmans.

Biochemistry and biophysics are very young sciences, still in their baby shoes. It was less than seven decades ago (1903) that Büchner discovered that cell-free filtrates of yeast could ferment sugar, which meant that biological reactions could be separated from life and be analyzed. When my beloved teacher Sir Frederick Gowland Hopkins had set out to study the production of lactic acid in muscle contraction he was told that biochemistry is a "*contradictio ad absurdum*," an impossibility, because as soon as we break down the system it is not alive any more.

We have penetrated deeply into cellular mechanisms and begin even to ask questions about the origin of life. In my opinion the study of the cell can lead us a long way in that direction too. Life has developed its processes gradually, never rejecting what it has built, but building over what has already taken place. As a result, the cell resembles the site of an archeological excavation with the successive strata on top of one another, the oldest one the deepest. The older a process, the more basic a role it plays and the stronger it will be anchored, the newest processes being dispensed with most easily. This is why in division the cell reverts to simpler, more archaic processes of energy production.

Where biochemistry and biophysics will lead us nobody can predict. They may change our life more than all the other sciences already have.

My own scientific career was a descent from higher to lower dimension, led by the desire to understand life. I went from animals to cells, from cells to bacteria, from bacteria to molecules, from molecules to electrons. The story had its irony, for molecules and electrons have no life at all. On my way life ran out between my fingers. The present book is the result of my effort to find my way back again, climbing up the same ladder I so laboriously descended. Having started in medicine, it is befitting that I should end with a medical problem, cancer, which took away most of what was dear to me.

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II

WATER, THE HUB OF LIFE

Life originated in the ocean. Water is its *mater* and *matrix*, mother and medium. Life could leave the ocean when it learned to grow a skin and take the water with it. We are still water animals, only we have the water inside, not outside. We are a walking aquarium. We are a 20% aqueous solution. We have guarded our legacy, the water of the sea, carefully. The ionic concentrations of our blood still reflect the ionic concentrations of the primordial ocean. It is a remarkable fact that we have probably kept these concentrations more constant than the ocean itself, which has since changed.

When a biochemist studies a system his first question is "What is it made of?" Life, having originated in the ocean, could build its machinery only from what it found there. It found three things: water, organic molecules (including CO_2), and ions. No structures could be built of ions. With their charge and motility they could be used only as triggers, or for balancing electric or osmotic differences. Water, as we know it from everyday experience, is a shapeless, unreactive, neutral liquid. So, according to biology today, life's machinery is built of organic matter using water as its medium.

Sixty years of research has taught me to look upon water as part and parcel of the living machinery, if not the hub of life. Water is the most extraordinary substance! Practically all its properties are anomalous, which enabled life to use it as building material for its machinery. Life is water dancing to the tune of solids. That biologists forgot about it is no more than natural. According to Sir Oliver Lodge the last thing a deep sea fish could discover is water.

The extraordinary nature of water is borne out by the two constants used most frequently for the characterization of substances: melting and boiling points. According to the size of its molecules, water should boil at 0°C. It boils at 100°C. It should melt at −100°C. It melts at 0°C, indicating that the water molecules tend to stick together. We have to decrease the temperature only by 1/273, cooling it from 273°K to 272°K, and water turns into a solid which can split rocks. Eskimos build their houses with it.

The unique shape of the water molecule is roughly represented in Fig. 1 (Horne, 1969). Being essentially a cloud of electrons, its outlines are not as sharp as suggested by the figure. In rapid rotation it would appear as a ball of about 3.8 Å. This queer, four-legged creature has a bend in the middle. Two of its legs are formed by its two H's, which give to their half of the molecule a positive charge enabling it to act as H donor forming two hydrogen bonds with other water molecules. The other two legs are formed by the nonbonded electron pairs of oxygen which lend to this end a negative charge, making the molecule a strong dipole, with a tetrahedral shape, enabling it to form two H bonds as acceptor with two other water molecules or whatever H donors there may be. The water molecule is thus capable of forming four H bonds of considerable strength of about 6 calories each. Each water molecule can thus bind four water molecules, each of which, in turn, can also bind four molecules. This entails that below 0°C water as a whole turns into one single continuous solid. The dipole character of the molecules may lead to more extensive structures. In many ways, the situation is analogous to a weak magnet which, if placed in iron filings, will polarize the nearby particles which, in turn, will polarize their neighbors, thus enabling extensive structures to be built up along the magnetic lines. In the case of water these structures may be stabilized by the H bond formation. The building up and breaking down of these structures will have a cooperative character.

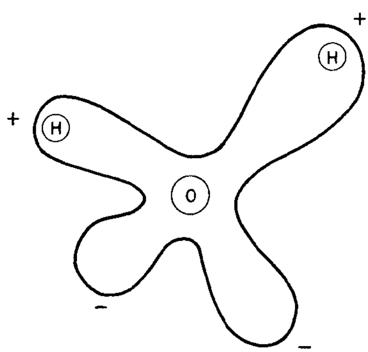

Fig. 1. Shape of the water molecule. Redrawn from R. A. Horne's "Marine Chemistry" (Horne, 1969).