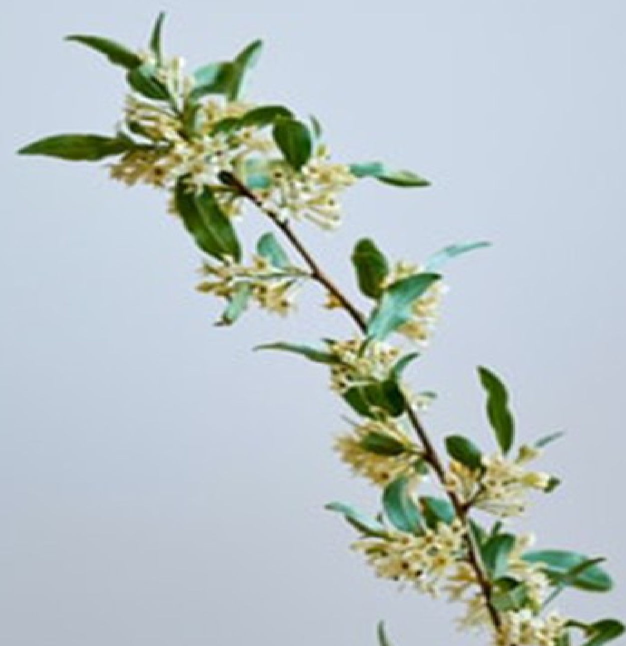
JACQUES LOEB



THE ORGANISM AS A WHOLE, FROM A PHYSICOCHEMICAL VIEWPOINT

Jacques Loeb

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PREFACE

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It is generally admitted that the individual physiological processes, such as digestion, metabolism, the production of heat or of electricity, are of a purely physicochemical character; and it is also conceded that the functions of individual organs, such as the eye or the ear, are to be analysed from the viewpoint of the physicist. When, however, the biologist is confronted with the fact that in the organism the parts are so adapted to each other as to give rise to a harmonious whole; and that the organisms are endowed with structures and instincts calculated to prolong their life and perpetuate their race, doubts as to the adequacy of a purely physicochemical viewpoint in biology may arise. The difficulties besetting the biologist in this problem have been rather increased than diminished by the discovery of Mendelian heredity, according to which each character is transmitted independently of any other character. Since the number of Mendelian characters in each organism is large, the possibility must be faced that the organism is merely a mosaic of independent hereditary characters. If this be the case the question arises: What moulds these independent characters into a harmonious whole?

The vitalist settles this question by assuming the existence of a pre-established design for each organism and of a guiding “force” or “principle” which directs the working out of this design. Such assumptions remove the problem of accounting for the harmonious character of the organism from the field of physics or chemistry. The theory of natural selection invokes neither design nor purpose, but it is incomplete since it disregards the physicochemical constitution of living matter about which little was known until recently.

In this book an attempt is made to show that the unity of the organism is due to the fact that the egg (or rather its cytoplasm) is the future embryo upon which the Mendelian factors in the chromosomes can impress only individual characteristics, probably by giving rise to special hormones and enzymes. We can cause an egg to develop into an organism without a spermatozoön, but apparently we cannot make a spermatozoön develop into an organism without the cytoplasm of an egg, although sperm and egg nucleus transmit equally the Mendelian characters. The conception that the cytoplasm of the egg is already the embryo in the rough may be of importance also for the problem of evolution since it suggests the possibility that the genus- and species-heredity are determined by the cytoplasm of the egg, while the Mendelian hereditary characters cannot contribute at all or only to a limited extent to the formation of new species. Such an idea is supported by the work on immunity, which shows that genus- and probably species-specificity are due to specific proteins, while the Mendelian characters may be determined by hormones which need neither be proteins nor specific or by enzymes which also need not be specific for the species or genus. Such a conception would remove the difficulties which the work on Mendelian heredity has seemingly created not only for the problem of evolution but also for the problem of the harmonious character of the organism as a whole.

Since the book is intended as a companion volume to the writer's former treatise on *The Comparative Physiology of the Brain* a discussion of the functions of the central nervous system is omitted.

Completeness in regard to quotation of literature was out of the question, but the writer notices with regret, that he has failed to refer in the text to so important a contribution to the subject as Sir E.A. Schäfer's masterly presidential address on "Life" or the addresses of Correns and Goldschmidt on the determination of sex. Credit should also have been given to Professor Raymond Pearl for the discrimination between species and individual inheritance.

The writer wishes to acknowledge his indebtedness to his friends Professor E.G. Conklin of Princeton, Professor Richard Goldschmidt of the Kaiser Wilhelm Institut of Berlin, Dr. P.A. Levene of the Rockefeller Institute, Professor T.H. Morgan of Columbia University, and Professor Hardolph Wasteneys of the University of California who kindly read one or more chapters of the book and offered valuable suggestions; and he wishes especially to thank his wife for suggesting many corrections in the manuscript and the proof.

The book is dedicated to that group of freethinkers, including d'Alembert, Diderot, Holbach, and Voltaire, who first dared to follow the consequences of a mechanistic science—incomplete as it then was—to the rules of human conduct and who thereby laid the foundation of that spirit of tolerance, justice, and gentleness which was the hope of our civilization until it was buried under the wave of homicidal emotion which has swept through the world. Diderot was singled out, since to him the words of Lord Morley are devoted, which, however, are more or less characteristic of the whole group.

J. L.

THE ROCKEFELLER INSTITUTE
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The Organism as a Whole

CHAPTER I

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INTRODUCTORY REMARKS

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1. The physical researches of the last ten years have put the atomistic theory of matter and electricity on a definite and in all probability permanent basis. We know the exact number of molecules in a given mass of any substance whose molecular weight is known to us, and we know the exact charge of a single electron. This permits us to state as the ultimate aim of the physical sciences 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 non-living world the goal of biology can be expressed in the same way.

This idea has more or less consciously prevailed for some time in the explanation of the single processes occurring in the animal body or in the explanation of the functions of the individual organs. Nobody, not even a scientific vitalist, would think of treating the process of digestion, metabolism, production of heat, and electricity or even secretion or muscular contraction in any other than a purely chemical or physicochemical way; nor would anybody think of explaining the functions of the eye or the ear from any other standpoint than that of physics.

When the actions of the organism as a whole are concerned, we find a totally different situation. The same physiologists who in the explanation of the individual processes would follow the strictly physicochemical viewpoint and method would consider the reactions of the organism as a whole as the expression of non-physical agencies. Thus Claude Bernard,[1] who in the investigation of the individual life processes was a strict mechanist, declares that the making of a harmonious organism from the egg cannot be explained on a mechanistic basis but only on the assumption of a "directive force." Bernard assumes, as Bichat and others had done before him, that there are two opposite processes going on in the living organism: (1) the phenomena of vital creation or organizing synthesis; (2) the phenomena of death or organic destruction. It is only the destructive processes which give rise to the physical manifestations by which we judge life, such as respiration and circulation or the activity of glands, and so on. The work of creation takes place unseen by us in the egg when the embryo or organism is formed. This vital creation occurs always according to a definite plan, and in the opinion of Bernard it is impossible to account for this plan on a purely physicochemical basis.

> There is so to speak a pre-established design of each being and of each organ of such a kind that each phenomenon by itself depends upon the general forces of nature, but when taken in connection with the others it seems directed by some invisible guide on the road it follows and led to the place it occupies....
>
> We admit that the life phenomena are attached to physicochemical manifestations, but it is true that the essential is not explained thereby; for no fortuitous

> coming together of physicochemical phenomena constructs each organism after a plan and a fixed design (which are foreseen in advance) and arouses the admirable subordination and harmonious agreement of the acts of life....
>
> We can only know the material conditions and not the intimate nature of life phenomena. We have therefore only to deal with matter and not with the first causes or the vital force derived therefrom. These causes are inaccessible to us, and if we believe anything else we commit an error and become the dupes of metaphors and take figurative language as real.... Determinism can never be but physicochemical determinism. The vital force and life belong to the metaphysical world.

In other words, Bernard thinks it his task to account for individual life phenomena on a purely physicochemical basis —but the harmonious character of the organism as a whole is in his opinion not produced by the same forces and he considers it impossible and hopeless to investigate the "design." This attitude of Bernard would be incomprehensible were it not for the fact that, when he made these statements, the phenomena of specificity, the physiology of development and regeneration, the Mendelian laws of heredity, the animal tropisms and their bearing on the theory of adaptation were unknown.

This explanation of Bernard's attitude is apparently contradicted by the fact that Driesch[2] and v. Uexküll,[3] both brilliant biologists, occupy today a standpoint not very different from that of Claude Bernard. Driesch assumes that there is an Aristotelian “entelechy” acting as directing guide in each organism; and v.Uexküll suggests a kind of Platonic “idea” as a peculiar characteristic of life which accounts for the purposeful character of the organism.

v. Uexküll supposes as did Claude Bernard and as does Driesch that in an organism or an egg the ultimate processes are purely physicochemical. In an egg these processes are guided into definite parts of the future embryo by the Mendelian factors of heredity—the so-called genes. These genes he compares to the foremen for the different types of work to be done in a building. But there must be something that makes of the work of the single genes a harmonious whole, and for this purpose he assumes the existence of “supergenes.”4 v.Uexküll’s ideas concerning the nature of a Mendelian factor and of the “supergenes” are expressed in metaphorical terms and the assumption of the “supergenes” begs the question. The writer is under the impression that this author was led to his views by the belief that the egg is entirely undifferentiated. But the unfertilized egg is not homogeneous, on the contrary, it has a simple but definite physicochemical structure which suffices to determine the first steps in the differentiation of the organism. Of course, if we suppose as do v.Uexküll and Driesch that the egg has no structure, the development of structure becomes a difficult problem—but this is not the real situation.

2. Claude Bernard does not mention the possibility of explaining the harmony or apparent design in the organism on the basis of the theory of evolution, he simply considers the problem as outside of biology. It was probably clear to

him as it must be to everyone with an adequate training in physics that natural selection does not explain the origin of variation. Driesch and v.Uexküll consider the Darwinian theory a failure. We may admit that the theory of a formation of new species by the cumulative effect of aimless fluctuating variations is not tenable because fluctuating variation is not hereditary; but this would only demand a slight change in the theory; namely a replacement of the influence of fluctuating variation by that of equally aimless mutations. With this slight modification which is proposed by de Vries,[5] Darwin's theory still serves the purpose of explaining how without any pre-established plan only purposeful and harmonious organisms should have survived. It must be said, however, that any theory of life phenomena must be based on our knowledge of the physicochemical constitution of living matter, and neither Darwin nor Lamarck was concerned with this. Moreover, we cannot consider any theory of evolution as proved unless it permits us to transform at desire one species into another, and this has not yet been accomplished.

It may be of some interest to point out that we do not need to make any definite assumption concerning the mechanism of evolution and that we may yet be able to account for the fact that the surviving organisms are to all appearances harmonious. The writer pointed out that of all the 100,000,000 conceivable crosses of teleost fish (many of which are possible) not many more than 10,000, *i.e.*, about one-hundredth of one per cent., are able to live and propagate. Those that live and develop are free from the grosser type of disharmonies, the rest are doomed on account of a gross lack of harmony of the parts. These latter we never see and this gives us the erroneous conception that harmony or “design” is a general character of living matter. If anybody wishes to call the non-viability of 9999/100 per cent. of possible teleosts a process of weeding out by “natural selection” we shall raise no objection, but only wish to point out that our way of explaining the lack of design in living nature would be valid even if there were no theory of evolution or if there had never been any evolution.

3. v. Uexküll is perfectly right in connecting the problem of design in an organism with Mendelian heredity. The work on Mendelian heredity has shown that an extremely large number of independently transmissible Mendelian factors help to shape the individual. It is not yet proven that the organism is nothing but a mosaic of Mendelian factors, but no writer can be blamed for considering such a possibility. If we assume that the organism is nothing but a mosaic of Mendelian characters it is difficult indeed to understand how they can force each other into a harmonious whole[6]; even if we make ample allowance for the law of chance and the corresponding wastefulness in the world of the living. But it is doubtful whether this idea of the rôle of Mendelian factors is correct. The facts of experimental embryology strongly indicate the possibility that the cytoplasm of the egg is the future embryo (in the rough) and that the Mendelian factors only impress the individual (and variety) characters upon this rough block. This idea is supported by the fact that the first development—in the sea urchin to the gastrula stage inclusive—is independent of the nucleus, which is the bearer of the Mendelian factors. Not before the skeleton or

mesenchyme is formed in the sea urchin egg is the influence of the nucleus noticeable. This has been shown in the experiments of Boveri in which an enucleated fragment of an egg was fertilized with a spermatozoön of a foreign species. If this is generally true, it is conceivable that the generic and possibly also the species characters of organisms are determined by the cytoplasm of the egg and not by the Mendelian factors.

In any case, we can state today that the cytoplasm contains the rough preformation of the future embryo. This would show then that the idea of the organism being a mosaic of Mendelian characters which have to be put into place by “supergenes” is unnecessary. If the egg is already the embryo in the rough we can imagine the Mendelian factors as giving rise to specific substances which go into the circulation and start or accelerate different chemical reactions in different parts of the embryo, and thereby call forth the finer details characteristic of the variety and the individual. The idea that the egg is the future embryo is supported by the fact that we can call forth a normal organism from an unfertilized egg by artificial means; while it is apparently impossible to cause the spermatozoön to develop into an organism outside the egg.

4. The influence of the whole on the parts is nowhere shown more strikingly than in the field of regeneration. It is known that pieces cut from the plant or animal may give rise to new growth which in many cases will restore somewhat the original organism. Instead of asking what is the cause of this so-called regeneration we may ask, why the same pieces do not regenerate as long as they are parts

of the whole. In this form the mysterious influence of the whole over its parts is put into the foreground. We shall see that growth takes place in certain cells when certain substances in the circulation can collect there. The mysterious influence of the whole on these parts consists often merely of the fact that the circulating specific or non-specific substances—we cannot yet decide which—will in the whole be attracted by certain spots and that this will prevent them from acting on other parts of the organism. If such parts are isolated the substances can no longer flow away from these parts and the parts will begin to grow. It thus becomes utterly unnecessary to endow such organisms with a “directing force” which has to elaborate the isolated parts into a whole.

5. The same difficulty which we have discussed in regard to morphogenesis exists also in connection with those instincts which preserve the life of the organism and of the race. The reader need only be reminded of all the complicated instincts of mating by which sperm and eggs are brought together; or those by which the young are prevented from starvation to realize the apparently desperate problems in store for a mechanist, to whom the assumption of design is meaningless. And yet we are better off in regard to our knowledge of the instincts than we are in regard to morphogenesis, as in the former we can show that the apparent instincts in some cases obey simple physico-chemical laws with almost mathematical accuracy. Since the validity of the law of gravitation has been proved for the solar system the idea of design in the motion of the planets has lost its usefulness, and this fact must serve us as a

guide wherever we attempt to put science beyond the possibility of mysticism. As soon as we can show that a life phenomenon obeys a simple physical law there is no longer any need for assuming the action of non-physical agencies. We shall see that this has been accomplished for one group of animal instincts; namely those which determine the relation of animals to light, since these are being gradually reduced to the law of Bunsen and Roscoe. This law states that the chemical effect of light equals the product of intensity into duration of illumination. Some authors object to the tendency toward reducing everything in biology to mathematical laws or figures; but where would the theory of heredity be without figures? Figures have been responsible for showing that the laws of chance and not of design rule in heredity. Biology will be scientific only to the extent that it succeeds in reducing life phenomena to quantitative laws.

Those familiar with the theories of evolution know the extensive rôle ascribed to the adaptations of organisms. The writer in 1889 called attention to the fact that reactions to light—*e.g.*, positive heliotropism—are found in organisms that never by any chance make use of them; and later that a great many organisms show definite instinctive reactions towards a galvanic current—galvanotropism—although no organism has ever had or ever will have a chance to be exposed to such a current except in laboratory experiments. This throws a different light upon the seemingly purposeful character of animal reactions. Heliotropism depends primarily upon the presence of photosensitive substances in the eye or the epidermis of the organism, and these substances are inherited regardless of whether they are useful or not. It is only a metaphor to call reactions resulting from the presence of photosensitive substances “adaptation.” In this book other examples are given which show that authors have too often spoken of adaptation to environment where the environment was not responsible for the phenomena. The blindness of cave animals and the resistance of certain marine animals to higher concentrations of sea water are such cases. Cuénot speaks of “preadaptation” to express this relation. The fact is that the “adaptations” often existed before the animal was exposed to surroundings where they were of use. This relieves us also of the necessity of postulating the existence of the inheritance of acquired characters, although it is quite possible that the future may furnish proof that such a mode of inheritance exists.

6. We have mentioned that according to Claude Bernard two groups of phenomena occur in the living organism: (1) the phenomena of vital creation or organizing synthesis (especially in the egg and during development); (2) the phenomena of death or organic destruction. These two processes are briefly discussed in the first and last chapters.

These introductory remarks may perhaps make it easier for the reader to retain the thread of the main ideas in the details of experiments and tables given in this book.

CHAPTER II

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THE SPECIFIC DIFFERENCE BETWEEN LIVING AND DEAD MATTER AND THE QUESTION OF THE ORIGIN OF LIFE

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1. Each organism is characterized by a definite form and we shall see in the next chapter that this form is determined by definite chemical substances. The same is true for crystals, where substance and form are definitely connected and there are further analogies between organisms and crystals. Crystals can grow in a proper solution, and can regenerate their form in such a solution when broken or injured; it is even possible to prevent or retard the formation of crystals in a supersaturated solution by preventing "germs" in the air from getting into the solution, an observation which was later utilized by Schroeder and Pasteur in their experiments on spontaneous generation. However, the analogies between a living organism and a crystal are merely superficial and it is by pointing out the fundamental differences between the behaviour of crystals and that of living organisms that we can best understand the specific difference between non-living and living matter. It is true that a crystal can grow, but it will do so only in a supersaturated solution of its own substance. Just the reverse is true for living organisms. In order to make bacteria or the cells of our body grow, solutions of the split

products of the substances composing them and not the substances themselves must be available to the cells; second, these solutions must not be supersaturated, on the contrary, they must be dilute; and third, growth leads in living organisms to cell division as soon as the mass of the cell reaches a certain limit. This process of cell division cannot be claimed even metaphorically to exist in a crystal. A correct appreciation of these facts will give us an insight into the specific difference between non-living and living matter. The formation of living matter consists in the synthesis of the proteins, nucleins, fats, and carbohydrates of the cells, from the split products. To give an historical example, Pasteur showed that yeast cells and other fungi could be raised on the following sterilized solution: water, 100gm., crystallized sugar, 10gm., ammonium tartrate, 0.2gm. to 0.5gm., and fused ash from yeast, 0.1gm.[7] He undertook this experiment to disprove the idea that protein or organic matter in a state of decomposition was needed for the origin of new organisms as the defenders of the idea of spontaneous generation had maintained.

2. That such a solution can serve for the synthesis of all the compounds of living yeast cells is due to the fact that it contains the sugars. From the sugars organic acids can be formed and these with ammonia (which was offered in the form of ammonium tartrate) may give rise to the formation of amino acids, the "building stones" of the proteins. It is thus obvious that the synthesis of living matter centres around the sugar molecule. The phosphates are required for the formation of the nucleins, and the work of Harden and

Young suggests that they play also a rôle in the alcoholic fermentation of sugar.

Chlorophyll, under the influence of the red rays of light, manufactures the sugars from the CO_2 of the air. This makes it appear as though life on our planet should have been preceded by the existence of chlorophyll, a fact difficult to understand since it seems more natural to conceive of chlorophyll as a part or a product of living organisms rather than the reverse. Where then should the sugar come from, which is a constituent of the majority of culture media and which seems a prerequisite for the synthesis of proteins in living organisms?

The investigations of Winogradsky on nitrifying,[8] sulphur and perhaps also on iron bacteria have to all appearances pointed a way out of this difficulty. It seemed probable that there were specific micro-organisms which oxidized the ammonia formed in sewage or in the putrefaction of living matter, but the attempts to prove this assumption by raising such a nitrifying micro-organism on one of the usual culture media, all of which contained organic compounds, failed. Led by the results of his observations on sulphur bacteria it occurred to Winogradsky that the presence of organic compounds stood in the way of raising these bacteria, and this idea proved correct. The bacteria oxidizing ammonia to nitrites were grown on the following medium; 1gm. ammonium sulphate, 1gm. potassium phosphate, 1gm. magnesium carbonate, to 1 litre of water. From this medium, which is free from sugar and contains only constituents which could exist on the planet before the appearance of life, the nitrifying bacteria were able to form sugars, fatty acids, proteins, and the other specific constituents of living matter. Winogradsky proved, by quantitative determination, that with the nitrification an increase in the amount of carbon compounds takes place. “Since this bound carbon in the cultures can have no other source than the CO_2 and since the process itself can have no other cause than the activity of the nitrifying organism, no other alternative was left but to ascribe to it the power of assimilating CO_2.”[9] “Since the oxidation of NH_3 is the only source of chemical energy which the nitrifying organism can use it was clear *a priori* that the yield in assimilation must correspond to the quantity of oxidized nitrogen. It turned out that an approximately constant ratio exists between the values of assimilated carbon and those of oxidized nitrogen.” This is illustrated by the results of various experiments as shown in Table I.

TABLE I

	No. 5	No. 6	No. 7	No. 8
	mg.	mg.	mg.	mg.
Oxidized N	722.0	506.1	928.3	815.4
Assimilated C	019.7	015.2	026.4	022.4
Ratio N:C	036.6	033.3	035.2	036.4

It is obvious that 1 part of assimilated carbon corresponds to about 35.4 parts oxidized nitrogen or 96 parts of nitrous acid.

These results of Winogradsky were confirmed in very careful experiments by E.Godlewski, Sr.[10]

The nitrites are further oxidized by another kind of micro-organisms into nitrates and they also can be raised without organic material.

Winogradsky had already previously discovered that the hydrogen sulphide which is formed as a reduction product from $CaSO_4$ or in putrefaction by the activity of certain bacteria can be oxidized by certain groups of bacteria, the sulphur bacteria. Such bacteria, *e.g.*, *Beggiatoa*, are also commonly found at the outlet of sulphur springs. They utilize the hydrogen sulphide which they oxidize to sulphur and afterwards to sulphates, according to the scheme:

(1) $2H_2S + O_2 = 2H_2O + S_2$
(2) $S_2 + 3O_2 + 2H_2O = 2H_2SO_4$

The sulphuric acid is at once neutralized by carbonates.

Winogradsky assumes that the oxidation of H_2S by the sulphur bacteria is the source of energy which plays the same rôle as the oxidation of NH_3 plays in the nitrifying bacteria, or the oxidation of carbon compounds—sugar and others—in the case of the other lower and higher organisms. Winogradsky has made it very probable that sulphur bacteria do not need any organic compounds and that their nutrition may be accomplished with a purely mineral culture medium, like that of the nitrite bacteria. On the basis of this assumption they should also be able to form sugars from the CO_2 of the air.

Nathanson[11] discovered in the sea water the existence of bacteria which oxidize thiosulphate to sulphuric acid. They will develop if some $Na_2S_2O_3$, is added to sea water.

These bacteria can only develop if CO_2 from the air is admitted or when carbonates are present. For these organisms the CO_2 cannot be replaced by glucose, urea, or other organic substances. Such bacteria must therefore possess the power of producing sugar and starch from CO_2 without the aid of chlorophyll. Similar observations were made by Beijerinck on a species of fresh-water bacteria.[12]

Finally the case of iron bacteria may briefly be mentioned though Winogradsky's views are not accepted by Molisch.

We may, therefore, consider it an established fact that there are a number of organisms which could have lived on this planet at a time when only mineral constituents, such as phosphates, K, Mg, SO_4, CO_2, and O_2 besides NH_3, or SH_2, existed. This would lead us to consider it possible that the first organisms on this planet may have belonged to that world of micro-organisms which was discovered by Winogradsky.

If we can conceive of this group of organisms as producing sugar, which in fact they do, they could have served as a basis for the development of other forms which require organic material for their development.

In 1883 the small island of Krakatau was destroyed by the most violent volcanic eruption on record. A visit to the islands two months after the eruption showed that "the three islands were covered with pumice and layers of ash reaching on an average a thickness of thirty metres and frequently sixty metres."[13] Of course all life on the islands was extinct. When Treub in 1886 first visited the island, he found that blue-green algæ were the first colonists on the pumice and on the exposed blocks of rock in the ravines on the mountain slopes. Investigations made during subsequent expeditions demonstrated the association of diatoms and bacteria. All of these were probably carried by the wind. The algæ referred to were according to Euler of the nostoc type. Nostoc does not require sugar, since it can produce that compound from the CO_2 of the air by the activity of its chlorophyll. This organism possesses also the power of assimilating the free nitrogen of the air. From these observations and because the *Nostocaceæ* generally appear as the first settlers on sand the conclusion has been drawn that they or the group of *Schizophyceæ* to which they belong formed the first settlers of our planet.[14] This conclusion is not quite safe since in the settlement of Krakatau as well as in the first colonizing of sand areas the nature of the first settler is determined chiefly by the carrying power of wind (or waves and birds).

We may now return from this digression to the real object of our discussion, namely that the nutritive solutions of organisms must be very dilute and consist of the split products of the complicated compounds of which the organisms consist. The examples given sufficiently illustrate this statement.

The nutritive medium of our body cells is the blood, and while we take up as food the complicated compounds of plants or animals, these substances undergo a digestion, *i.e.*, a splitting up into small constituents before they can diffuse from the intestine into the blood. Thus the proteins are digested down to the amino acids and these diffuse into the blood as demonstrated by Folin and by Van Slyke. From here the cells take them up. The different proteins differ in regard to the different types of amino acids which they contain. While the bacteria and fungi and apparently the higher plants can build up all their different amino acids from ammonia, this power is no longer found in the mammals which can form only certain amino acids in their body and must receive the others through their food. As a consequence it is usually necessary to feed young animals on more than one protein in order to make them grow, since one protein, as a rule, does not contain all the amino acids needed for the manufacture of all the proteins required for the formation of the material of a growing animal.15

3. The essential difference between living and non-living matter consists then in this: the living cell synthetizes its own complicated specific material from indifferent or non-specific simple compounds of the surrounding medium, while the crystal simply adds the molecules found in its supersaturated solution. This synthetic power of transforming small "building stones" into the complicated compounds specific for each organism is the "secret of life" or rather one of the secrets of life.

What clew have we in regard to the nature of this synthetic power? We know that the comparatively great velocity of chemical reactions in a living organism is due to the presence of enzymes (ferments) or to catalytic agencies in general. Some of these catalytic agencies are specific in the sense that a given catalyzer can accelerate the reaction of only one step in a complicated chemical reaction. While these enzymes are formed by the action of the body they can be separated from the body without losing their catalytic efficiency. It was a long time before scientists succeeded in isolating the enzyme of the yeast cell which causes the alcoholic fermentation of sugar; and this gave rise to the premature statement that it was not possible to isolate this enzyme since it was bound up with the life of the yeast cell. Such a statement was even made by a man like Pasteur, who was usually a model of restraint in his utterances, and yet the work of Buchner proved him to be wrong.

The general mechanism of the action of the hydrolyzing enzymes is known. The old idea of de la Rive, that a molecule of enzyme combines transitorily with a molecule of substrate; the further idea, which may possibly go back to Engler, that the molecule of substrate is disrupted in the "strain" of the new combination and that the broken fragments fall off or are easily knocked off by collision from the ferment molecule which is now ready to repeat the process, seems to be correct. On the assumption that the velocity of enzyme reaction is proportional to the mass of the enzyme and that de la Rive's idea was correct, Van Slyke and Cullen were able to calculate the coefficients of the velocity of enzyme reactions for the fermentation of urea and other substances, and the agreement between calculated and observed values was remarkable.[16]

While the hydrolytic action of enzymes is thus clear the synthesis in the cell is still a riddle. An interesting suggestion was made by van't Hoff, who in 1898 expressed the idea that the hydrolytic enzymes should also act in the opposite direction, namely synthetically. Thus it should not only be possible to digest proteins with pepsin but also to synthetize them from the products of digestion with the aid of the same enzyme. This expectation was based on the idea that the enzyme did not alter the equilibrium between the hydrolyzed and non-hydrolyzed part of the substrate but only accelerated the rate with which the equilibrium was reached. Van't Hoff's idea omitted, however, the possibility that in the transitory combination between enzyme molecule and substrate a change in the molecular configuration of the substrate or in the distribution of intramolecular strain may take place. The first apparently complete confirmation of van't Hoff's suggestion appeared in the form of the synthesis of maltose from grape sugar by the enzyme maltase, which decomposes maltose into grape sugar. By adding the enzyme maltase from yeast to a forty per cent. solution of glucose Croft Hill[17] obtained a good yield of maltose. It turned out, however, that what he took for maltose was not this compound but an isomer, namely isomaltose, which has a different molecular configuration and cannot be hydrolyzed by the enzyme maltase.

Lactose is hydrolyzed from kephyr by an enzyme lactase into galactose and glucose; by adding this enzyme to galactose and glucose a synthesis was obtained not of lactose but of isolactose; the latter, however, is not decomposed by the enzyme lactase.

E. F. Armstrong has worked out a theory which tries to account for this striking phenomenon by assuming "that the enzyme has a specific influence in promoting the formation of the biose which it cannot hydrolyze."[18] The theory is very ingenious and seems supported by fact. This then would lead to the result that certain hydrolytic enzymes may have a synthetic action but not in the manner suggested by van’t Hoff.

The principle enunciated by Armstrong, that in the synthetic action of hydrolytic enzymes not the original compound but an isomer is formed which can not be hydrolyzed by the enzyme, may possibly be of great importance in the understanding of life phenomena. It shows us how the cell can grow in the presence of hydrolytic enzymes and why in hunger the disintegration of the cell material is so slow. It was at first thought that the formation of isomers contradicted the idea of the reversible action of enzymes, but this is not the case; on the contrary, it supports it but makes an addition which may solve the riddle of what Claude Bernard called the creative action of living matter. We shall come back to this problem in the last chapter.

Kastle and Loevenhart demonstrated the synthesis of a trace of ethylbutyrate by lipase if the latter enzyme was added to the products of the hydrolysis of ethylbutyrate, ethyl alcohol, and butyric acid by the same enzyme.[19] Taylor[20] obtained the synthesis of a slight amount of triolein by the addition of the dried fat-free residue of the castor bean to a mixture of oleinic acid and glycerine.... No synthesis occurred with acetic, butyric, palmitic, and stearic acids with glycerine, mannite, and dulcite, and the experiments with the last two alcohols and oleinic acid likewise yielded no synthesis.

This suggests possibly a specific action of the enzyme. If this slight reversible action had any biological significance (which might be possible, since in the organism secondary favourable conditions might be at work which are lacking *in vitro*) there should be a parallelism between masses of lipase in different kinds of tissues and fat synthesis. Loevenhart indicated that this might be a fact, but a more extensive investigation by H.C. Bradley has made this very dubious.[21]

Very little is known concerning the reversible action of the hydrolytic protein enzymes. A.E. Taylor digested protamine sulphate with trypsin and found that after adding trypsin to the products of digestion a precipitate was formed after long standing; and we may also refer to experiments of Robertson with pepsin on the products of caseinogen to which we shall return in the next chapter. It therefore looks at present as if van't Hoff's idea of reversible enzyme action might hold in the modification offered by Armstrong. It remains doubtful, however, whether this reversibility can explain all the synthetic processes in the cell. No objection can be offered at present if any one makes the assumption that each cell has specific synthetic enzymes or some other synthetic mechanisms which are still unknown.