A CHEMICAL CONCEPT OF THE ORIGIN AND DEVELOPMENT OF LIFE[1]

A PRELIMINARY PRESENTATION

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The concept of the origin and development of life which as a result of your kind invitation I am to present to you this evening, has not been evolved from my inner consciousness but has resulted from more than twenty years of experimentation in my laboratory modified by the work of others. In the nineties I was seeking a method by which I might obtain large quantities of some low form of life free from contamination. This quest ended in my devising my large bacterial tanks, with which I was able to secure pure bacterial substance by the kilogram and was able to demonstrate the following fundamental facts.

1. Bacterial substance consists of glyconucleoprotein.
2. It contains no cellulose, consequently bacteria are not plants.
3. Bacterial substance shows no differentiation into cytoplasm, nucleus, or nucleolus and undergoes no mitosis, consequently bacteria are not "cells" as the morphologists would interpret this term.
4. On cleavage with acid or alkali, bacterial substance yields carbohydrates, amino-acids and purine bases.
5. It may be split into poisonous and nonpoisonous portions, with evidence that the cleavage follows definite chemical lines.
6. Dead pathogenic bacterial substance kills animals with the same symptoms and like lesions to those which follow inoculation with the living organism. Therefore the symptoms and lesions

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of a disease such as typhoid fever are not due directly to the growth of these bacilli in the patient's body but result from the cleavage of the bacterial substance by some agency supplied by the body of the host.

7. Nonpathogenic bacterial substance furnishes as much poison as does the pathogenic. Therefore, immunity to certain organisms cannot be due to the absence of poison in these organisms but must be explained in some other way.

8. Vegetable and animal proteins such as edestin from hemp seed and casein from milk contain as much poison as do the pathogenic bacilli.

9. All proteins contain a poisonous group. It will be understood that none of these poisons are active when given by mouth and are so only when introduced parenterally. This is because protein cleavage in the alimentary canal is different from that occurring in the blood and tissues.

I may add that the above statements in all essentials have been verified by workers in this country, France and Germany. I published them in book form in 1913. I am not tonight going farther into the details of my experimental work but will devote my time to the conclusions which I have drawn. Even with this limitation I can only present a preliminary outline, awaiting opportunity to write in further detail.

THE ORIGIN OF LIFE

How can we differentiate between non-living and living matter? What is the earliest manifestation of the acquisition of life? Certainly matter does not cease to be matter when it becomes endowed with life. An atom of nitrogen in ammonia is still nitrogen when it is incorporated in a more complicated protein molecule. I can say with much confidence that the conversion of non-living into living matter is accompanied by increased molecular lability. By this I mean that the atoms or electrons within the molecule are energized. Their orbits are enlarged. Within their orbits they move with greater speed. Their chemism is intensified so greatly that they are now able to drag into their orbits atoms and possibly molecules which have hitherto been beyond their grasp. In other words the molecules begin feeding on outside matter. All living things absorb, assimilate and eliminate. This means that metabolism or trading in energy begins. Such is the first evidence of life. Have we any idea of the nature of these primitive living molecules? Yes. They were and are protein molecules. There is no life save in proteins. These are polymers of amino-acids. The amino-acids, at least the simplest of them, have been and are today being formed under proper environmental conditions from inorganic substances. Furthermore, each protein differs from all others in its content, kind or position in the molecule, of amino-acids. Up to the present time less than twenty of these bodies have been found in nature but with this small number, numberless proteins are formed, much as all the words in our language are formed by varied groupings of the twenty-six letters in our alphabet. Simple proteins yield only alpha-amino-acid on hydrolysis.

In my opinion simple proteins are not living. There must be in the living molecular structure a carbohydrate group thus converting a simple protein into a gluco-protein. I have found two carbohydrates in bacterial substance. One of these which exists in some bacteria to the extent of 10 per cent, I believe to be attached to the nuclein group, while the other is attached to the nitrogen. With this glyco-protein we have a battery and this begins to operate under proper stimuli such as heat, light, electricity or the chemical constituents of something in the medium in which the molecular battery exists. In other words the stimulus is some form of energy. What causes the amino-acids to be synthesized I do not know. Emil Fischer has however synthesized amino-acids and has obtained a product which closely resembles natural protein.

Irritability or re-activity as Ralph Lillie prefers to call it, has long been known as a universal property of living matter. This means that the rate at which energy is received and discharged by the living protein may be altered, increased or decreased, by external stimuli which may be brought into contact with it. The stimulus may be in the form of food or fuel which brings to the organism, or the living system as the morphologist calls it, energy in the potential form, which is then discharged in the kinetic form. Metabolism is regulated by environment. Reaction between the organism and its environment is essential to all living matter. Without this, life cannot originate or having originated continue indefinitely. One can conceive of a piece of chalk or a lump of carbon existing indefinitely without reacting with its environment, without absorbing or eliminating, but one cannot conceive of a bacterium or a yeast cell retaining life indefinitely under these circumstances. I am fond of repeating a statement first employed I believe by Allen, "Living matter differs from dead in that the former trades in energy while the latter does not."

Still another attribute of living matter is its ability to reproduce itself. As I conceive it, the early forms of life must be particulate, not necessarily as this term is understood by the morphologist, but in a chemical sense, meaning that living matter maintains its molecular identity in no matter what form or environment it exists. The early forms of life must at the same time be small, microscopic or ultramicroscopic because the reaction between the organism and its environment can occur only when the reacting bodies are brought into immediate contact. This holds true whether we consider the lowest or the highest forms of life, whether we subscribe to the cellular or a chemical theory of the origin of life. In man, the highest form of life, contact is just as intimate, the food material being brought to the cells by the blood and lymph. This holds whether the energy be brought to the organism in the potential or kinetic form. There can be no question as to the nature and manner of reproduction in the lowest forms of life since we can see and study it in low forms such as bacteria. Reproduction occurs by fission.

If we assume that there was an Azoic period in the history of the earth, a period in which life even in its simplest forms did not exist, and we must assume this if we will accept the geologist's concept of the origin of the earth, then it follows of necessity that there was a certain time at which life on earth began. The evidence today indicates that energy derived from the sun is the original source of life. The chief difference between inanimate and animate matter is in its energy content. The forces in the sun's rays have energized dead matter into life. Perhaps, as suggested by Mathews the bulk of this energy is carried by the oxygen atoms within the molecule. As to what was the form of this first life we can but conjecture, but from the evidence, some of which I have just presented you, I believe that we are safe in assuming that life as such did not exist before the evolution of the protein molecule. Every element which makes up the protein molecule exists also in the inorganic chemical world. There was a time when organic chemical compounds did not yet exist. Henry, referring to the possibility of artificial production of organic compounds, wrote, "It is not probable that we shall ever attain the power of imitating nature in these operations. For in the functions of a living plant a directing principle appears to be concerned, peculiar to animated bodies, and superior to and differing from the cause which has been termed chemical affinity." And yet only a short time after this Wöhler succeeded in synthesizing urea.

Moore and Webster appear to have succeeded in synthesizing formaldehyde from carbon dioxide and moisture under the influence of ultraviolet rays and in the presence of an inorganic colloid. It matters not whether as has been suggested by von Baeyer, formaldehyde was the first organic substance produced in nature leading toward the development of life. The point is that it has been shown that organic substances may be synthesized in the laboratory from inorganic substances and that such simple organic structures as amino-acids may be synthesized experimentally into compounds closely resembling natural proteins. It makes no difference whether we can now or ever will be able to reproduce each and every step to the ultimate development of life. Failure in no way invalidates our hypothesis any more than our inability to build a star or planet disproves existing views as to the probable structure of the universe.

At some stage in the evolution of life the cell as we know it today came into existence. It is back to this point that the morphologist traces the origin of living matter and beyond this he does not allow himself to go. The doctrine "omnis cellula ex cellula" may perhaps hold after the first cell came into being but the chemist cannot accept the cell as the lowest or the original manifestation of life. Nearly twenty years ago I first stated my belief that life is fundamentally chemical and may, indeed probably does exist in simpler and less tangible forms than the living cell or even the living bacterium which I do not regard as a true cell for it contains no differentiated cytoplasm and nucleus.

It becomes incumbent upon the chemist who denies the contentions of the morphologist to explain how the cell may evolve from simpler forms of life. This we cannot yet do but the work of DuNouy on the surface equilibria of colloids opens interesting fields for speculation. This author presents evidence that the most probable configuration of equilibrium in a protein colloid solution is in the form of a cell. This would present a minimum of free energy compatible with the total energy. If a microscopic droplet of protein solution is sprayed into the air the constituent molecules of this droplet will proceed to arrange themselves in thermodynamic equilibrium, with relation to each other. In this process the droplet will become coated with a surface layer of protein three hundred or four hundred times more viscous than the interior. If the droplet has a diameter of ten microns, equilibrium may be established within four seconds. If the diameter is but three microns, equilibrium is established in about one second. If equilibrium has been established before the droplet completes its fall the concentrated surface layer will be strong enough to maintain its shape even if it strikes a dry surface. The presence of carbon dioxide or hydrochloric acid gas or ultraviolet rays suffices to render some of the constituents of the protein layer insoluble, thus enabling the droplet to keep its individuality even though it fall into pure water. Assuming as I have stated before that energy and its transformation is one of the dominant characteristics of life, we have evidence in the work of DuNouy that the cell may be but the logical consequence of the tendency of the protein molecule or molecules to establish dynamic equilibrium.

What is the smallest form of living substance known? The smallest living structure known today is that entity which has been described and studied in greatest detail by d'Herelle and to which he has given the name of bacteriophage. This living particulate chemical substance is much smaller than the smallest known cell and bears out my hypothesis first stated nearly twenty years ago. d'Herelle gives to the bacteriophage the generic name protobe or first life. It is without doubt the simplest form of life known today but I regard it as not proven that the first life was not even simpler.

The bacteriophage fulfills all the criteria of life. It can assimilate in a heterologous medium, transforming a heterologous substance into homologous bacteriophage substance, a substance distinctively its own. With this function of assimilation it also possesses the function of adaptation to changing environment. Furthermore it possesses the faculties of reproduction and variability. The substance is antigenic, has the chemical constitution of protein, possesses as great and prolonged viability as bacterial spores and appears to be an electro negative colloid just as are the majority of the bacterial species. The dimensions of the bacteriophage corpuscle are approximately those of the serum globulin micella, its diameter being about twenty millimicrons. The substance appears to be thermolabile, its virulence being destroyed at about 75°. The protein micella is the colloidal unit. It is the smallest possible particle of matter in the colloidal state. Possibly as d'Herelle states it is the unit of living matter and cells are constituted of a union of micellae. The bacteriophage is of about the size of a micella.

BACTERIA

I do not regard bacteria as the simplest form of life. Their chemical structure is very complicated. They are essentially nucleins and their chief function is to multiply. Whether the individual consists of a single or many molecules I do not know. Probably their structure is multimolecular but if so the chemism between the molecules must be very strong. I know of no way of distinguishing between intermolecular and intramolecular activity.

Bacteria will live under most diverse conditions. They will grow in a medium which contains organic nitrogen only in the form of ammonia. They continue to live or at least to retain life under wide ranges of temperature. When food is scarce they go into a resting or spore stage. They multiply by fission. In them acquired characters such as increased or decreased virulence are transmitted. They are antigenic and can be shown susceptible to classification in groups by their antigenic reactions.

While the bacterial cell is morphologically simple in structure, it is as complex in chemical composition as are the cells of the animal body. I know of no work done since I reached this conclusion which throws any doubt upon it. The conclusion that I would draw therefrom is either that bacteria are already relatively high up in the scale of life or else that even the simplest forms of life consist of relatively complex aggregations of protein molecules.

The general constancy and immutability of bacterial types is illustrated in the history of epidemic disease. Generally speaking these diseases run true to type through their recorded history, be this short or long. Tubercle bacilli found in Egyptian mummies present the same characteristics and cause the same type of tissue destruction as do tubercle bacilli in the consumptive of today. The characteristic symptoms and lesions of smallpox observed and described by Indian writers before the Christian era show no essential variation from those which manifest themselves in the unprotected individual of today. Through all the centuries there has been no important mutation in the smallpox virus, nor any marked modification in its behavior when introduced into the human body. The most ancient descriptions of the plague are so plainly indicative of the disease as we know it in the present generation that there can be no mistake of the identity of the virus of this disease in most ancient times with that of the present. The pneumonias of today are marked by the same seasonal variation, characterized by the same modes of onset, by like avenues of progress, and by similar results with those seen and described by Hippocrates. Because bacteria and protozoa are low forms of life it has been assumed that they are especially liable to marked mutations involving alterations in chemical composition, and what is of more importance, so far as pathogenic organisms are concerned, in their effect upon man. In my opinion the assumption that bacteria and protozoa readily undergo mutation is not warranted by any facts which can be gathered in a study of the history of infectious diseases. I am ready to assert that there has been less mutation in the tubercle bacillus or the virus of smallpox since the beginning of recorded time than there has been in man and the other higher animals.

We do not know the nature of the filterable viruses such as that of smallpox but it is possible that they are of the nature of protobes such as d'Herelle's bacteriophage. There is some evidence that as time goes on we will be able to establish a more definite connection or association between the protobes and bacteria. In the case of the tubercle bacillus for instance there is evidence that ultrafiltrates of the tubercle bacillus contain what appears to be a living virus and the evidence suggests that this is a small granular form of the tubercle bacillus. As to whether this is a tubercle bacillus micella we can only surmise.

THE CHEMISTRY OF PARASITISM

Having outlined my concept, a chemical concept, of the early development of life I desire now to present to you my interpretation of the manner in which life became differentiated into its many forms. My understanding of this complex phenomenon, as I have said, is not based upon pure philosophic induction but upon experimental observation in my own laboratory. Before discussing the origin of species therefore, I must summarize briefly my conception of the life processes as I have observed them in bacteria.

The chief function of life is self perpetuation. If this function is to continue active, the living substance must be so situated that it can procure nutritive material from its immediate environment. While energy is furnished in the available carbohydrates and fats and while water and certain minerals are requisite, the structural and reproductive requirements of the protein molecule are met only by protein material, of which the basis is the amino-acid. All living substances are proteins. The nature of the protein differs for every different type of life. This difference is due to variation in the number, nature or intramolecular arrangement of the constituent amino-acids. There may be other differences which present methods have not as yet enabled us to recognize. If the necessary pabulum were always available as pure amino-acids and in the correct proportions for the particular living cell, the matter would be simple. However, as a rule the available organic food supply consists of combinations of amino-acids in varying degrees of complexity, up to the complete protein molecule.

In order that the living substance, let us say a bacterium, may assimilate this food it first becomes necessary to disrupt the heterologous protein molecule into its constituent amino-acids so that these may be absorbed and built up into the bacterial structure. Bacteria secrete enzymes or ferments for this purpose. So do all living cells. These ferments will digest certain proteins but not all proteins. If a living cell is in contact with a foreign protein against which it does not possess a digestive ferment it will gradually evolve a ferment specific for that protein. I believe it to be a fundamental law that a living cell in contact with a foreign protein will evolve an enzyme to destroy that protein. Many years ago Duclaux showed that penicilliun glaucum grown on starch produces invertase only. On lactose it produces lactase in addition. On milk it elaborates a proteoclastic enzyme. The ability of living cells to produce specific enzymes to meet the necessity for disrupting the substrate with which they come in contact is essential to existence both under normal and abnormal conditions. It enables the cells to feed upon assimilable substances and to destroy injurious ones. The ease with which living cells may function in these directions is dependent upon many and varied factors such as temperature, physical and chemical conditions, the activity of the cell which is seeking to feed or protect itself and the constitution of the body upon which it acts. Here lie many problems awaiting future investigation.

Much remains to be learned of the nature of ferments or enzymes. They are particles of matter, some of them wholly simple like spongy platinum, others highly complex like the yeast ferment or pepsin or trypsin. Enzymes are inanimate storehouses of energy which may be brought into action under proper environment or on coming under the influence of certain physical or chemical stimuli. They may be compared roughly to storage batteries. Ferments may be protein but are not animate.

In the same way that the bacterium will elaborate a digestive enzyme, so also will the body cell do this when it comes in contact with a foreign protein. The typhoid bacillus on entrance into the body grows luxuriantly during the incubation period, for in the blood it finds an abundance of available food material in the same simple form that is available for the body cells. Living typhoid bacilli have been found in the blood of man during the incubation period, before any symptoms of the disease have become manifest. The germ is converting body proteins or at least the amino-acids of the blood into typhoid bacillus protein. The reaction is synthetic and there are no symptoms. But the body cells have been stimulated by the presence of a foreign protein and in about ten days they have elaborated a ferment or enzyme which will break down this foreign protein. As soon as this defense reaction becomes well developed disease becomes manifest. Now, typhoid bacilli are being destroyed, the process is analytic, the protein poison is being liberated.

During the incubation period the process is constructive. After the body cells have learned to elaborate a ferment which will destroy the typhoid bacillus the process in turn becomes destructive and in this destruction the protein poison appears to be liberated. This poison I have found to be present in every protein which I have so far examined. It exists not alone in pathogenic bacteria but also in the nonpathogenic and even in such otherwise innocuous proteins as egg white and the proteins of the cereal grains. Indeed edestin from hemp seed and casein from milk, and egg white furnished me the largest and most satisfactory amounts of protein poison. While I have been unable to obtain this substance in anything approaching a pure state, it appears to contain many amino-acids and, apparently should be classed as a polypeptid. It is only poisonous when administered parenterally, for alimentary digestion apparently further breaks it up into the simple amino-acids. In the case of typhoid fever which I have used as an example the symptoms result from the liberation of the protein poison. The severity of the disease depends upon the amount and rapidity of liberation of the poison. The very small doses of the poison which will produce serious symptoms experimentally indicate its possession of a high degree of energy. In my opinion it kills by tearing off from certain body cells secondary and functioning chemical groups.

The perpetuation of life depends upon the ability of living substance to convert heterologous proteins into homologous proteins. This holds equally for the higher forms of life for if in the case under consideration the human body is unable to convert typhoid proteins into human protein, the result will be disastrous. True, this conversion is of itself not without danger.

The ability of a bacterium to produce disease after it has entered an animal depends mainly upon two factors. First it must be able to establish for itself a parasitic existence in its host. It must be able to sustain itself and multiply its kind on the pabulum within its reach. Second, there must be no destructive enzyme already existing in the body tissues, against this particular bacterium. Disease depends in great part upon how abundantly a given microörganism may multiply in the tissues before the body cells have completed the elaboration of a destructive enzyme. Where one is already in existence the bacterium is destroyed at once and only an infinitesimal amount of poison is liberated. No symptoms result. The seriousness of the symptoms depends upon the amount of poison liberated and the rapidity of its liberation. Of course, there are other factors in certain diseases such as location within the body, the secretion of a toxin by the bacterium and the like.

THE ORIGIN OF SPECIES

Let us now take up a consideration of those factors which may have had a bearing in the origin of species. At this point

I am not so interested in the inheritance of identical characteristics as I am in the inheritance of altered or acquired characteristics for it is by virtue of the latter that new species develop. I find no great difficulty in understanding that living substance might readily reproduce itself in its entirety but I am highly interested in the intimation that it can produce another living substance different from any that has been known previously.

I have said that the characteristics of bacteria have remained remarkably constant throughout the history of disease. There is an exception, one which I believe to be of fundamental importance in the development of species. I have said that the tubercle bacillus as it occurs in man appears to have undergone no remarkable change through recorded history. This is quite true but at the same time there is a tubercle bacillus which infects fowls which is not quite the same germ and yet another which infects cattle. Dr. Calmette has at the Pasteur Institute in Paris a strain of tubercle bacillus which he has cultivated artificially for over thirteen years and which appears to have lost entirely its ability to infect man and the lower animals.

The constancy of bacterial types and indeed of all living substances depends upon a relatively unchanging environment. In the lower forms of life environment has a very definite influence upon the characteristics of life. Furthermore, alterations in the structure of the protein molecule resultant on environmental changes may be and are inherited. A microörganism living in a milieu in which the pabulum is readily assimilated and transformed into homologous proteins will thrive. If, on the other hand, the environment is one in which the available food material is of widely different constitution from that of the living substance, continued existence will depend upon the ability of the microörganism to elaborate a ferment capable of disintegrating the foreign protein or protein-like substance into its constituent amino-acids so that they may be available for assimilation. If some of these amino-acids are deficient in quantity for the particular living substance, continued existence will now depend upon the ability of the living structure to adapt itself to this deficiency. If such an adaptation is made, there will result a change in the make-up of the living protein molecule.

While I am emphasizing chemical factors I am not unmindful that physical and other factors also play a part. I can readily understand why many species of animals and of plants have disappeared. No species can continue when it ceases to receive and utilize energy from its environment. A change of a few degrees in the annual average temperature might change markedly the flora and fauna of the area in which it occurs. Climatic factors are more readily recognized in the higher forms of life, but I shall continue to limit myself to the effect of changes in the chemical environment on the lower forms of life.

The presence and availability of new or different amino-acids or similar protein radicles will ultimately determine an alteration in the constitution of the living protein molecule. If this alteration in environment is permanent the altered constitution of the living molecule will likewise become permanent and will remain so as long as the environment is relatively the same. The development of new species in the lowest forms of life depends upon physico chemical alterations in the environment. The persistence of new species so formed is dependent upon the permanency of the environmental changes.

A streptococcus highly pathogenic for the horse will on repeated passage through a laboratory animal such as the mouse or rabbit or guinea pig, gradually lose its high virulence for the horse while acquiring an increased invasive power against that animal through which it is being passed. That there is an actual change in the chemical constitution of this streptococcus is indicated by the fact that after several passages its antigenic power as a horse streptococcus which was originally of high titer becomes completely lost.

Not only this but it has been found that cultivation of a streptococcus in an artificial medium containing the blood of some laboratory animal increases the virulence of the streptococcus against this particular animal. Furthermore the antigenic characteristics of this streptococcus are altered after repeated growth on these special laboratory media. Thus we may speak of a horse streptococcus, a mouse or rabbit or guinea pig streptococcus all derived from the same ancestor, each of them still a streptococcus, but definitely altered in chemical nature by their immediate nutritive environment.

d'Herelle believes that there is but one bacteriophage but that this like the streptococcus just described is capable of adaptation to growth in a wide variety of bacterial hosts. The Shiga bacteriophage and the Staphylo-phage differ from each other in their predilection, one for the dysentery bacillus and the other for the staphylococcus. These are their foods of choice and they find it difficult to grow on other bacteria. However, adaptation may be accomplished and it is possible to change the Shiga-phage into the Staphylo-phage and vice versa. There is an almost limitless possible number of bacteriophages dependent upon the degree of invasiveness for different bacteria but the evidence presented by d'Herelle would indicate that this is a matter of adaptation to the environment on the part of a single original bacteriophage.

This adaptation is so complete that it involves an alteration in the chemical structure of the bacteriophage which can be recognized in changes in its antigenic properties. Shiga-phage actually becomes chemically different from the Staphylococcus bacteriophage. Alterations in the environment have produced a new species which will maintain its identity as long as the environment remains essentially unchanged. Further environmental changes will produce yet other alterations in the structure of the living molecule, not necessarily a reversion to the original structure but perhaps with the development of an entirely new and more complex structure to suit the requirements of the altered nutritive environment.

Many of the higher forms of life contain two or more proteins no one of which can be said to be more specific than the other for that particular living substance. Such a simple plant as wheat for example contains gliadin, globulin, glutenin, proteose and leucosin, five proteins in all. Now wheat glutenin appears to be similar in its chemical constitution with the glutenin found in barley and in rye. I would interpret this as highly suggestive evidence that wheat, barley and rye evolved from the same primordial ancestor. Environmental changes, possibly variations in the nutritonal resources, have been responsible for the differentiation of these three grains. The farmer of today knows well the importance of environment. With the same seed, the same heredity, he does not anticipate an equally good or abundant crop in every field in different years. The fertility of the soil, the amount of sun and rain and many other environmental factors play a most important part. If some of these factors are disadvantageous to the continued existence of a grain, this grain must either adapt itself to changed conditions which it will do with alterations in its own structure and appearance, or it must eventually die out.

In forms of life such as those which we have just been discussing, in which two or more different proteins exist together, we must conceive as possible that species differentiation does not necessarily entail complete change in any or all of the constituent proteins but that in these higher forms new proteins may be added, possibly by differentiation of the original with the result that the new protein and the original both exist in the same living substance. Where a protein has at last been evolved which best fits the functional needs and where its environment remains little changed, its chemical constitution will remain remarkably constant. It is said that the proteins of the lens of the eye are different from the other proteins of the body but are identical in the lenses of a wide variety of animals. Here there is little environmental change for the environment is not the outside world but the blood and lymph.

I have mentioned changes in antigenic properties as indicating alterations in the makeup of the protein molecule. The question might be raised as to whether such changes do necessarily indicate alterations in the constitution of the molecule. The term antigen is employed by immunologists to designate those substances which when introduced into the animal body parenterally lead to the elaboration within the treated animal of a substance which antagonizes or tends to neutralize its own action. Up to the present the weight of evidence is all that antigens are proteins. Moreover it appears that each protein leads to the elaboration of a specific antibody. Thus an animal treated with the venom of a certain species of snake produces an antibody to this venom and not to the venoms of other species of snakes. The toxin of the diphtheria bacillus produces a diphtheria antitoxin and this has no antagonistic action on other toxins. Each antigen acts specifically and the nature of the antibody formed is strictly specific. The body cells appear to elaborate these antibodies and they do it for self protection. Some of the antibodies neutralize their specific antigen by combining with them and thus rendering them inert. This seems to be true of the antitoxins of diphtheria and tetanus also for vegetable toxins such as those of abrin and ricin and the venoms of snakes. In other cases the antibody renders its antigen inert by disrupting it into its harmless constituents. Could there be better or more conclusive evidence of the ability of the body cells to adapt themselves to their environment and to protect themselves against threatened destruction? Living cells are capable of being trained or educated. In other words their behavior may be modified by changed environment.

It has been shown that the specificity of antigens is dependent upon their chemical composition. For instance there are in milk four chemically distinct proteins and each is capable of causing the body cells to elaborate its own specific antibody. In egg proteins there are three chemically distinct proteins some of which are common to the eggs of different species of birds while others are found in a single or in a limited number of species. It seems to be true that the specificity of an antigen is determined by the location of some aromatic radicles within the structure of the protein molecule. When proteins are hydrolyzed they lose their antigenic properties. My students and I showed many years ago that gelatin which is a hydrolyzed protein and devoid of certain aromatic radicles such as tyrosin and tryptophan, and which contains only a trace of phenylalanin is not an antigen. Like results have been obtained by subjecting true proteins to the cleavage action of digestive ferments such as trypsin and pepsin. Likewise the protamins, which are complexes of diamino-acids, and wanting in the amino-acids, are not antigenic. Free amino-acids are not antigenic. All antigens are colloids, all apparently are proteins. Now, it has been found that certain chemicals, as formaldehyde, nitrous acid, and iodin, may be introduced into the protein molecule without destruction of its antigenic properties, but the antibodies elaborated are specific to the altered proteins and not to the original substances. Some years ago Obermeyer and Pick found that the serum of rabbits treated with proteins which had been radically changed by being iodized or nitrified did not precipitate the native protein but did act upon the altered protein with which the animal had been treated.

All life is protein and the development of new species is due to molecular re-arrangement in the structure of the protein molecule. Something is added or subtracted, or chemical groups within the molecule are rearranged. The recently discovered facts demonstrated by the precipitin and sensitization tests make this certain. By these, proteins may be positively identified either when mixed or unmixed with other proteins. Group relationship may be shown by these methods and up to the present time in no other way. Especially is this true when the results of these tests are measured quantitatively. The proteins of the hen's egg sensitize guinea pigs to themselves and to a lesser degree to the proteins of the eggs of other birds. The proteins of man's blood sensitize animals to themselves and less perfectly to those of the blood of the anthropoid apes. Wheat, rye and barley all come from a common plant and under different environments have developed into three species. In this way varieties and species come into existance.

EVOLUTION IN THE HIGHER FORMS OF LIFE

From the lowest to the highest forms of life environment plays a part of greater or less significance in the development of species. These environmental factors may be chemical or they may be physical. I have presented to you my concept based upon the simpler forms of life for here that very simplicity facilitates more accurate study and interpretation.

In calling to your attention the primary importance of environment in the development of life and the differentiation of species, it is in no way my desire to intimate that I am not in accord with the prevailing doctrines of heredity. The discussion is along quite different lines for in the latter our interest is in phenomena in which gross alterations are conspicuously absent while in the former it is the alterations which are of chief importance and interest. The genes about which students of heredity are saying much I can accept, if I am permitted to regard these genes as atomic groups, some right handed, some left handed, in the specific protein which reproduces itself.

But I find no difficulty in recognizing the action of chemical environment even in the highest forms of life. Morphologists stress the stability of germ plasm but some of them do admit that certain poisons such as alcohol, lead, mercury, and syphilis may deleteriously affect the reproductive cells. In my opinion, even more striking examples might be given. A boy and a girl. born of healthy parents and raised to maturity under normal conditions may migrate into a goiterous district and after acquiring goiters may marry. Their children may be cretins. In this case it is the *absence*, according to the now accepted belief, of iodin in the food and drink which leads to this deterioration. Please understand that it is only the absence of one chemical element which causes this disaster. I am in favor of eugenics but I cannot forget that environment as well as heredity must be taken into consideration. The claim that the reproductive cells are not influenced by the somatic cells is one which I believe to be unwarranted. In seeding it is well to select sound grain, but the harvest will not be determined wholly by this, but will depend to some extent on the fertility of the soil.

What is the optimum relationship as between the chemical environment, particularly the food supply, and the living structure? Without considering other factors that undoubtedly play a part I would say that the more closely the heterologous protein resembles in its make-up the homologous living protein, the more nearly identical its content and proportion of the different amino-acids and associated radicles, the more constant will be the composition of the living molecule and the higher will be the degree of perfection which it will attain while remaining essentially unaltered chemically. I recognize that there are other essential requirements such as vitamines and the like but the basis of life is protein and in this thesis I have limited myself almost entirely to the consideration of the chemistry of the living protein molecule.

Some living forms such as bacteria feed upon other living forms. They can do so because they can convert and assimilate without difficulty the protein molecule of the host. I consider it possible that the more nearly the proteins of the host resemble chemically those of the invader the greater will be the pathogenicity of the latter. I suggest that some investigator study by the antigenic reactions, the protein relationships between parasite and host. In the case of bacteria, feeding upon man or animal, the objection might be raised that they derive their sustenance, not from the living molecules of the animal, but from the simpler protein food radicles and cleavage products present in the circulating blood and lymph. But this objection cannot hold in the case of test tube experiments in which the available pabulum consists of the tissues of the host.

One might infer that I believe that a cannibalistic existence would be the ideal form of life. But curiously enough even in such low forms of life as bacteria and bacteriophages, cannibalism appears not to exist. Protein molecules endowed with attributes of life, while apparently bent upon the destruction of other forms of life, particularly simpler forms, appear incapable of destroying living substances of identical or nearly identical chemical constitution. This is readily understandable. Where there are two such living substances in apposition, their chemisms would be identical, their spheres of influence the same, their tropisms would balance one another and the result would be no chemical reaction. A solution of ammonium chloride mixed with another solution of ammonium chloride remains ammonium chloride.

Late in the 18th century Lavoissier, scientist, patriot, martyr, showed the process of respiration in man is comparable to the burning of a candle. About 100 years ago, Wöhler made urea synthetically. A few years later Dunglisson and Emmett, in their scantily supplied laboratory at the University of Virginia announced that the free acid in the gastric juice of man is hydrochloric acid. Dumas in France, Liebig in Germany, and others continued to develop physiological chemistry. About the middle of the last century leading universities in this country provided chairs in this subject. For many years Chittenden at Yale was the standard bearer and on his retirement his good work was continued and amplified by Mendel. Splendid work in this subject has been done by Van Slyke, Lusk, Folin and others. Ehrlich and Hatta, after more than 600 attempts built up arsphenamine synthetically and this with its cogeners has done much to mitigate the plagues of syphilis and allied diseases.

Starling and others have discovered hormones and the brilliant results obtained by Banting in his discovery of insulin are well known. Abel not only discovered epinephrin, but determined its structural formula and it is now made synthetically. The same talented investigator appears to be on the high road to similar results in the study of insulin.

However, all these are inanimate substances and up to the present time no chemist has awakened dead matter into life. It may be that this will never be done. Whatever may be individual opinion on this subject, past, present and even future, failures should not prevent us from interrogating nature and learning so far as possible how she in her great laboratory with boundless facilities and with countless ages in which to operate has accomplished this great result. Without predictions as to what degree of knowledge future researches will reveal I have ventured to present my views on this subject. Should they, even in part, be confirmed the morphologist must radically change his teachings as to the relative importance of heredity and environment. I hold that the lowest forms of life have come into existence through chemical agencies and that environment has been a stronger factor in the evolution of life and in the development of the varieties and species than is believed by the biologist of today.

REFERENCES

Vaughan, Victor C.: Protein Split Products in Relation to Immunity and Disease. Lea & Febiger, 1913.

d'Herelle, F.: The Bacteriophage and Its Behavior. Williams and Wilkins, 1926.

duNouy, P. Lecomte: Surface Equilibria of Biological and Organic Colloids. Chemical Catalog Co., Inc., 1926.

Lereboullet, P., and Lelong, M.: Tuberculosis, Paris Medical, 1926, vol. 16, p. 1, January 7.

Lilly, Ralph S.: Protoplasmic Action and Nervous Action. University of Chicago Press, 1923.

Mathews, Albert P.: Some General Aspects of the Chemistry of Cells. General Cytology, University of Chicago Press, 1924.