SCIENCE

A WEEKLY JOURNAL DEVOTED TO THE ADVANCEMENT OF SCIENCE, PUBLISHING THE OFFICIAL NOTICES AND PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE

FRIDAY, FEBRUARY 14, 1908

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SOME OF THE PRESENT-DAY PROBLEMS OF BIOLOGICAL CHEMISTRY *

DURING the past few decades there has been gradually developing in the biological world a clearer recognition of the importance of a study of function, coupled with a fuller appreciation of the great diversity of the processes characteristic of life. It has come to be the fashion for naturalists—who up to comparatively recent times were content mainly to study form and structure—to turn their attention to observation of function, to learn how and why certain things are accomplished. Each decade has witnessed a broadening of the point of view; in botany, zoology, paleontology and geology new methods of investigation have been gradually applied, new relationships have been established, and the study of life, past and present, has taken on a new and broader significance. The Mendelian law and the present theories of genetics; the facts of modern cytology and the theories of heredity consequent thereto; the present-day experiments in breeding and variation with the conclusions to be drawn therefrom; the modern methods and theories of physiology in general; are the natural outcome of a progressive scientific activity where the study of function has come to occupy a prominent position and where the experi-

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* Address of the president of the American Society of Biological Chemists and chairman of the Biological Section of the American Chemical Society, at the joint meeting in Chicago, January 1, 1908.

mental method is being largely applied in biology as in the physical sciences.

The historical and descriptive study of biology has been gradually giving place to experiment. The zoologist is no longer content with systematic work, with the naming and classifying of species and genera, but he seeks to understand the chemical and physical changes that occur in growth, development, old age, death, etc.; or, in other words, he would know the cause or causes of these phenomena. He would understand the reason for things that occur during life, and with that end in view he turns to the experimental method, just as in physics and chemistry experimental or analytical study is made use of in the solving of problems that pertain to these sciences.

In botany, attention is being more and more directed to the study of plant physiology, with its chemical and physical problems. It is not enough to know that some species of fungi, for example, become black at a certain stage of their growth, but we need the explanation of the cause. The enzyme is to be detected and isolated, and the substance or substances upon which it acts identified. So, too, the many phenomena connected with the growth, nutrition and pathology of plants interest us, but knowledge of what is actually occurring can only be had by application of chemical methods. Systemic study of plants and animals will always be important, but if we are to have adequate explanation of the hundred and one phenomena characteristic of living forms we must turn our attention to experimental methods, as is being so largely done at the present time throughout the biological world, with due regard also to possible chemical transformations and reactions, that may be symbolical of broader changes in function and structure.

Descriptive embryology may tell us much regarding development, may show us the many different stages through which the egg, after fertilization, passes on its way to the full-fledged organism, but we gain thereby little or no insight into the causes that are operating to accomplish the ultimate end. We may well conjecture that in fertilization the spermatozoon brings in some chemical elements that constitute the exciting cause of cell division. Assuming such to be the case, we may ask whether it is a ferment substance of the ordinary enzyme type, or whether substances of a totally different character are involved. The answer to this question, however, does not concern us now; but that such a question is pertinent clearly suggests how the cause of cell cleavage may possibly be sought for in chemical or physico-chemical reactions incited by the admixture of germ and sperm substance.

It is well understood to-day that all the phenomena of life are to be explained on the basis of chemical and physical laws, and it is partly because of a clear recognition of this fact that biological chemistry has finally attained the eminence it has now reached as a division of biology; a branch of study that promises much in the ultimate explanation of many of the most intricate of the present-day problems of life. There is another reason why biological chemistry has shown such remarkable development during the past decades, and that is because of the direct aid it has furnished, and still promises to furnish, to physiology and to both experimental and practical medicine. Physiology as an independent science, having to do with the study of function, has grown in keeping with the increasing demand for wider knowledge of the processes of life, and this has led quite naturally to a broader recognition of the importance of the chemical side of physiology, since the physical side has been found inadequate to explain all the varied phenomena of living organisms. As a result, physiological chemistry has developed by leaps and bounds, until to-day special laboratories and journals devoted to this subject are to be found on all sides.

Again, in bacteriology, and in medicine in general, the applications of chemistry are so numerous and so fruitful in results that it is no longer necessary to defend the position of physiological or biological chemistry as a leading factor in the development of knowledge in these subjects. Sooner or later, in almost every problem that presents itself, we are brought face to face with some form of chemical reaction, or some chemical substance, upon which hinges the explanation of the phenomenon in question. Under the broad term of biological chemistry, we are dealing with a subject which, directly and indirectly, concerns itself with the chemical processes of living organisms, and as these are as many and varied as the organisms themselves, it is plain to see that the field is broad and one beset with many difficulties.

The very breadth of our field makes it clear that there will be diversity of opinion regarding the relative importance of the present-day problems in our science. To one man, quite naturally, a certain line of investigation will appeal most strongly, while to another a totally different set of problems will be suggested as the more important and promising. To one, questions of chemical structure and their bearing upon the processes of metabolism will prove most attractive; to another, questions of physico-chemical nature in their relationship to physiological processes in general will appeal most strongly; while to a third, the chemical dynamics or kinetics of physiological processes, the action of inorganic salts and their respective ions upon protoplasmic activity, etc., will seem the more promising field of work. In this latter field, we all recognize the great value of the results obtained in the laboratories here at Chicago, with equal recognition of the broad influence which the theories and conclusions drawn therefrom by Loeb, Mathews and others, have had upon the development and progress of this branch of our science.

Understanding fully the natural tendency of chemists and physiologists to differ somewhat in their estimate of the relative value of the different subjects calling for investigation, we may still, I think, readily select for discussion a certain number of problems in biological chemistry which we shall all recognize as being preeminently important to-day, and the settlement of which would go far toward giving a clearer understanding of many of the functions of the body. Among these problems stands out with startling distinctness the question of the chemical constitution of protein material. To the chemical mind interested in biological matters there is no problem that can overshadow this one in importance. As the basis of cell protoplasm of all kinds, protein stands forth as the one substance or class of substances absolutely essential for life. It is the chemical nucleus or pivot around which revolves a multitude of reactions characteristic of biological phenomena. In all the metabolic processes of animals and plants protein in some form plays a conspicuous part, and its many katabolic or decomposition products testify both to its complexity of structure and to the great diversity of reactions that may accompany its disintegration.

Nowhere is there to be found a better illustration of the physiological power which may reside in a certain definite grouping of elements than is seen in the case of protein. Gelatin, which resembles albumin in its superficial reactions and which contains approximately the same amount of nitrogen, is, as we know, quite incapable of taking the place of albumin in supplying the needs of the body for protein food. Yet, gelatin yields on decomposition many of the disintegration products furnished by albumin. Still, there are differences in the character and proportion of the cleavage products which, while not sufficiently marked to modify the ordinary protein color reactions, etc., are enough to indicate a difference in chemical structure, and owing to this difference in structure gelatin is quite unable to repair the waste of tissue in body metabolism. To every one at all familiar with protein chemistry the recent advances in knowledge of the hydrolytic cleavage products of this class of substances are more or less known. All proteins by appropriate methods of disintegration break down into a number of monoamino and diamino acids. Thirty years ago these hydrolytic cleavage products were represented mainly by leucine, tyrosine, aspartic and glutaminic acid; but now, as a result of efforts in many quarters, the number of such decomposition products has risen to at least seventeen. The significance of this statement is apparent when we remember that these cleavage products represent the building stones which make up the finished structure of the protein molecule, and if the time ever comes when we know all of these building stones, we shall then without doubt be able to construct or synthesize this most important substance.

Some of the most careful and painstaking work on the hydrolysis of proteins has been done in our own country by Dr. Thomas B. Osborne and his co-workers at New Haven. Examination of the results reported reveals several very important facts. Take, for example, some of the latest data afforded as in the hydrolysis of phaseolin,[1] the globulin of the kidney bean, formerly called legumin. Here, sixteen different cleavage products were identified and determined. The method of hydrolysis and the methods of separating the different amino acids were carried out by persons skilled by long practise and under the best of conditions, yet the percentage of total cleavage products determined amounted to only 54.27. Again, in the hydrolysis of excelsin,[2] the characteristic globulin of the Brazil-nut, the total yield of cleavage products was 61.09 per cent. Finally, in the hydrolysis of hordein,[3] the alcohol-soluble protein of barley, 71.32 per cent. of cleavage products was separated. In other words, by the best methods available and in the hands of skilled workers trained to take advantage of all the knowledge available, chemists are able at present to separate and identify only 54 to 71 per cent. of the total yield of cleavage products which results from the hydrolysis of protein. This undoubtedly means that there are still some building stones in the protein molecule with which as yet we are unfamiliar.

It needs no argument to convince any one that here lies a most important field of work; here is a problem the solution of which gives promise of rich reward, both to the chemist and to the physiologist. Of course, it is possible that the seventeen cleavage products referred to represent all the different types that are formed by hydrolysis and that the apparent deficiency is due simply to inadequate methods of separation. This, however, is not very probable, and it is to be noted in this connection that the results reported by Abderhalden and his co-workers in Germany are

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[1] *American Journal of Physiology*, Vol. XVIII., p. 295, 1907.

[2] *Ibid.*, Vol. XIX., p. 53, 1907.

[3] *Ibid.*, Vol. XIX., p. 117, 1907.

not radically different from those obtained by Osborne and others. Far more probable is it that there are still undiscovered a number of component parts of the protein molecule, knowledge of which must be obtained before we can hope to arrive at a synthesis of protein. Physiologists have long sought this goal. It means so much in the unraveling of many intricate problems in protein metabolism, in nutrition in general, in intracellular reactions and particularly those which bear upon the changes incidental to fertilization and cell division.

To how great degree the large variety of proteins of both animal and vegetable tissues have chemical and physiological individuality has long been an unsettled question. There is plenty of physiological evidence that the circulating proteins contained in the blood and lymph of different species of animals are unlike each other in some respects at least. Blood serum from one species introduced into the circulation of another species causes marked disturbance and even a fatal result. Animal proteins are plainly different in some respects from those of vegetable origin, while the latter derived from different sources vary greatly among themselves. We can readily conceive of individual proteins playing quite different parts in the nutrition of man and of animals when taken as food. There may be radical and logical differences in the nutritive value of animal as compared with vegetable proteins, although at present we have no positive proof of such differences. Arguments for or against vegetarianism, which are now based primarily upon questions of sentiment, may in time rest upon a solid foundation of fact. Such observations as have been made bearing upon the constitution of proteins are beginning to have special significance because of the radical differences in chemical make-up shown by the individual proteins studied. Take, for example, phaseolin from the kidney bean. This protein, as shown by both Osborne and Abderhalden, yields about 15 per cent. of glutaminic acid, 4 per cent. of lysine, 2.5 per cent. of proline, 5 per cent. of arginine, etc. Excelsin from the Brazil-nut, on the other hand, yields by hydrolysis 16 per cent. of arginine, 13 per cent. of glutaminic acid, 1.6 per cent. of lysine and 3.6 per cent. of proline; while the hordein of barley yields no lysine whatever, but furnishes 36 per cent. of glutaminic acid and nearly 14 per cent. of proline.

Such differences as these must have some significance; they certainly indicate a totally different assortment of building stones in the finished structure, and it is fair to presume that they carry with them some influence upon the physiological behavior of the proteins when the latter are taken as foods. The gliadin of wheat yields by hydrolysis about 37 per cent. of glutaminic acid, while the casein of cow's milk yields only 11 per cent. Here is indicated a radical difference in structure between the protein of animal origin and that derived from the plant kingdom. We can not say, however, that vegetable proteins are characterized by a high content of glutaminic acid, for while it may be true of both gliadin and hordein, it is not the case with phaseolin or excelsin, both of which yield only a little more glutaminic acid than animal casein. Plainly, we have here a problem not to be overlooked, and in these days of specialized vegetable foods we may justly expect an adequate explanation of the physiological significance to be attached to these chemical differences in structure. The gliadin of wheat, the zein of corn meal and the hordein of barley are all three alcohol-soluble proteins. This solubility in warm alcohol might well serve to place these proteins in a group by themselves, but they plainly are unlike chemically in some respects at least. There is harmony in the fact that all three yield no lysine by hydrolysis, but zein yields only 11 per cent. of glutaminic acid, while the other two furnish over 30 per cent. of this amino acid. Further, gliadin and hordein yield only about 2 per cent. of tyrosine, while zein furnishes 10 per cent. of this substance. To any one familiar with the known relationship between chemical constitution and physiological action as demonstrated in the study of drugs, the question as to what these differences in chemical constitution signify in the physiological action of three food proteins so closely related otherwise must be a pertinent one.

The present-day conception of the protein molecule is that it is a complex of different amino acids variously joined together. By energetic hydrolysis of the protein the latter is naturally broken apart into simple fragments represented by the monoamino and diamino acids. When the hydrolysis is carefully conducted as by a weak solution of trypsin, various proteoses result as the primary products, *i. e.*, high molecular polypeptides, which by further action of the enzymes may be successively broken down into simpler polypeptides, such as tetra-, tri- and dipeptides. Fischer and Abderhalden[4] a few years ago obtained a polypeptide in the pancreatic proteolysis of several proteins which was characterized by being composed solely of glycocoll, proline and phenylalanine. More recently Osborne and Clapp[5] obtained in the hydrolysis of gliadin what appeared to be a crystalline dipeptide composed of proline and phenylalanine. Further, Fischer and Abderhalden[6] have just described several dipeptides obtained in the partial hydrolysis of proteins; notably, glycocoll and l-tyrosine from silk, glycocoll and l-leucine from elastin and l-leucyl-d-glutaminic acid from gliadin; all characteristic dipeptides. In these results we see suggested the possibility of a primary cleavage of proteins into dissimilar polypeptides and dipeptides with distinct chemical make-up. If such reactions as these do occur, under the influence, for example, of pepsin or trypsin proteolysis, or even through the agency of the duodenal enzyme erepsin, then it is certainly reasonable to consider whether the individual proteoses or polypeptides formed during gastric and pancreatic digestion may not be endowed with different physiological properties. It raises the question whether in the digestion of protein in the gastro-intestinal tract by the enzymes naturally present there a kind of selective cleavage may not occur, in which the various amino acids contained in the protein are split off in special combinations representative of particular lines of attraction or union. Further, a tendency toward the formation of di- and polypeptides having a definite composition, assuming it to exist, may furnish a clue to the way in which the synthesis of protein may be accomplished. Obviously, however, there remains to be discovered first the nature of the 29–46 per cent. of the protein not yet represented by known decomposition products.

The well-known lability of the protein molecule accounts for the ease with which it undergoes hydrolysis, but it is, I think, quite plain that the ordinary cleavage of protein is not the result of a promiscuous breaking down of the molecule. On the contrary, there is satisfactory evidence that certain of the building stones are easily split off, while others are separated with greater difficulty and still others remain combined in large groups or masses,

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[4] *Zeitschrift für physiologischen Chemie*, Band XXXIX., p. 81, 1903.

[5] *American Journal of Physiology*, Vol. XVIII., p. 123, 1907.

[6] *Zentralblatt für Physiologie*, No. 15, p. 472, 1907.

thereby suggesting different degrees of attraction or union. Thus, it has been recently shown by Abderhalden and Voegtlin[7] that in the digestion of edestin by activated pancreatic juice certain of the amino acids are rapidly freed from their combinations, while others are liberated much more slowly; tyrosine, for example, was wholly free in two days' time, while glutaminic acid even at the end of sixteen days was split off only to the extent of two thirds of the amount present in the edestin molecule. The same has been found true in the pancreatic digestion of casein; tyrosine is rapidly and completely split off, glutaminic acid, on the other hand, very gradually. Thus, with casein and activated pancreatic juice the full amount of tyrosine contained in the protein was liberated in three days, while, as a rule, glutaminic acid could be obtained free only to the extent of 60–80 per cent. of the amount present and then only after three weeks of continued proteolysis. It is thought, though by no means settled, that alanine, valine, leucine, etc., behave exactly like glutaminic acid, while phenylalanine, proline and glycocoll do not admit of being freed from their combinations at all by the hydrolytic action of pancreatic juice. In other words, we see suggested here different degrees of attraction, different lines of combination among the many units entering into the construction of the protein molecule, which are well worthy of careful consideration, since they may have both chemical and physiological significance. It is no exaggeration to say that every additional fact bearing upon the nature and combinations of the chemical units present in the protein molecule promises to be of the greatest help in unraveling the many complexities now confronting us in our understanding of the nature of this most important substance.

Any consideration of protein cleavage as a physiological process naturally brings into the foreground enzymatic action in general, which is rapidly becoming recognized as the most important method of chemical change occurring in living organisms. We need go back only a few years when practically our knowledge of enzymatic action as it occurred in man and the higher animals was limited to the transformations of starch, protein and fat by the digestive juices of the gastro-intestinal tract, and in plants to the alteration of starch through diastase. But to-day what a change has come over our understanding of enzymolysis and how widespread the varied processes now included under this term! The bio-chemical reactions which are produced through the agency of the many enzymes so widely distributed in nature are not only numerous, but exceedingly varied in character, and we are practically justified in the assumption that the great majority of the intra- and extra-cellular chemical changes taking place in living organisms are the result of enzyme action. The old-time distinction between ferment action and the so-called vital action of living cells no longer carries weight. As is now well known, not hydrolysis merely, but oxidation, deamidization and a whole host of well-defined chemical changes, such, for example, as are characteristic of the different types of intermediary metabolism in the higher animals, are due to intra- and extra-cellular enzymes, formed, it is true, through the constructive power of living cells, but acting as simple chemical or physico-chemical agents and capable of producing their transformations whether in contact with the cells where they are formed or merely dissolved in suitable extracts free from tissue elements. Not only do these state-

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[7] *Zeitschrift für physiologischen Chemie,* Band XXXV., p. 315, 1907.

ments hold for the ordinary changes of tissue metabolism in animals and plants, but in that more or less hidden world of microorganisms so potent for good and evil, tangible enzymes are likewise responsible for many, if not all, of the chemical reactions by which the life and activity of the organisms are manifested. New enzymes and new forms of chemical change are constantly being discovered and as a result new light is being thrown upon many phases of tissue metabolism and the processes connected therewith.

Note, for example, the group of unique enzymes concerned in the transformations of nucleoproteins; enzymes which are widely distributed among different species of animals, in different organs and tissues, and which are truly unique in the character of the chemical changes they are capable of producing. Thus, we have nuclease, which splits off or liberates the purines from the nucleic acid complex; adenase and guanase, deamidizing enzymes which are able, by hydrolysis with liberation of ammonia, to form the oxypurines hypoxanthine and xanthine from the aminopurines adenine and guanine; xantho-oxidase, which by oxidation transforms the oxypurines to uric acid; and lastly, a uricolytic enzyme which is able to accomplish the destruction of uric acid with formation of allantoin as one of the intermediary products. Observe how these successive steps in the formation of uric acid from a nucleoprotein are accomplished by specific enzymes, each one of a distinct type and limited in its action to the one transformation. Further, it has been found by several observers that these characteristic enzymes are not common to all active tissues; different organisms show unlike equipment in this respect, thus indicating, as a recent writer has expressed it, that there are "noteworthy variations in the purine metabolism of different species."[8] Consider also arginase which has the power of effecting the hydrolysis of arginine, with production of urea and ornithine; an enzyme present in the liver, kidneys, thymus, intestinal mucous membrane and other tissues, as well as in yeast. Here is an enzyme, according to Dakin,[9] which is adapted for the exclusive hydrolysis apparently of dextro-arginine or of other substances containing the dextro-arginine grouping, and, as in the case of glucosides and sugars, the relation of the enzyme to the substrate is so intimately and finely adjusted that many other substances structurally similar to arginine are incapable of hydrolysis by arginase. Note likewise the newly discovered enzymes creatinase and creatininase,[10] the former of which is apparently able to transform creatin into creatinin, while the latter is said to decompose creatinin, presumably into methyl glycocoll and urea.

Truly, we have in the action of these peculiar enzymes a striking illustration of how in intermediary tissue metabolism successive chemical transformations may be accomplished in orderly fashion, while at the same time there is suggested the probable existence of many other specialized enzymes capable of inciting chemical reactions of equal interest. Is there not possible gain to be had in a broader, more comprehensive study of the intracellular enzymes of animal tissues? Doubtless in each species of animal there are peculiarities of metabolism which are truly specific; probably also there are specific enzymes, the presence and action of which are the determining factors in the special line of

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[8] Mendel and Mitchell, *American Journal of Physiology*, Vol. XX., p. 100, 1907.

[9] *Journal of Biological Chemistry*, Vol. III., p. 435, 1907.

[10] *Zeitschrift für physiologischen Chemie*, Band LII., p. 1, 1907.

metabolism occurring. Here is a field of work the cultivation of which promises results of the greatest value, while at the same time broadly applicable. Take, for example, the processes of growth as studied in the earlier stages of embryonic life upwards. What is the character of the processes by which the young organism is able to carry forward its rapid development? What the nature of the chemical changes in the construction and destruction of tissues constantly taking place during growth, where of necessity cell nucleoproteins are conspicuous elements? These questions can not be definitely answered at present, but some work carried on in our laboratory[11] at New Haven has indicated quite clearly the presence of certain specific enzymes early in embryonic life, while others common to the same organs in the full-grown animal are wholly wanting. Thus, it has been found in embryo pigs that the liver contains adenase, but no guanase; the latter enzyme, however, is present in the viscera of the embryo. Further, nuclease is present in the liver of the embryo, indicating that in the embryonic stage of this animal autolytic changes can take place in the liver; *i. e.*, a liberation of aminopurines from the nucleoproteins of the forming hepatic cells, while any adenine set free can be transformed by the deamidizing enzyme adenase into the oxypurine hypoxanthine. Likewise, any guanine liberated can by action of the guanase contained in the embryo viscera be transformed into xanthine. Here, however, reactions of this sort apparently stop in the embryo, at least of this particular species. The xantho-oxidase and the uricolytic enzyme are not present in the embryo, though quite abundant after birth. In other words, in the embryonic, growing organism, oxidative and katabolic enzymes which are obviously concerned in the gradual destruction of the purine part of the nucleic acid complex are wholly wanting; while those enzymes which have to do simply with transformation and alteration of the purines, thereby leading perhaps to the construction of added nuclein complexes, are conspicuous. Here, we see chemical evidence clearly substantiating our conception of the character of the transformations taking place in embryonic tissue; in the embryo, synthetical, constructive processes must naturally predominate, and the chemical mechanism present at that stage of development is designed solely to meet the requirements of synthesis and broad constructive power. Later on, however, when the embryo passes into an independent existence, those enzymes which have to do with katabolism gradually appear, and assume their function side by side with the enzymes primarily concerned in construction.

Problems of this character naturally lead us on to a consideration of the chemical aspects of fertilization, cell division, and the relative significance of the cytoplasm and karyoplasm of the egg and sperm cells in heredity, etc. As is well known, the head of the spermatozoon is essentially a cell nucleus, and like other nuclei is composed mainly of nucleoproteins; viz., compounds of nucleic acid with protein material of a more or less basic character. The only substance to be noted in addition is a small admixture of an organic iron compound known as karyogen. The nucleoproteins of the spermatozoon nucleus differ, however, from the corresponding substances present in the somatic cell nuclei in that the protein part of the molecule is made up mainly of some peculiar form of protein such as protamine, which Kossel has defined as the simplest type of protein material known.

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[11] "Chemical Studies on Growth," Mendel and Mitchell, *American Journal of Physiology*, Vol. XX., p. 115, 1907.

These protamines, of which salmine, clupeine, scombrine and sturine are types, are composed chiefly of diamino acids. Thus, as Kossel and Dakin[12] have shown, salmine contains 89.2 per cent. of its nitrogen as arginine, 4.3 per cent. as proline, 3.25 per cent. as serine, and 16.5 per cent. as valine; a total of 98.4 per cent. Similarly, scombrine contains 88.82 of its nitrogen as arginine, 3.8 per cent. as proline, and 6.8 per cent. as alanine; a total of 99.42 per cent. Sturine, on the other hand, differs from the two preceding protamines in that in addition to arginine it contains fairly large amounts of histidine and lysine. From these statements it is plain to see that the basic character of protamines with their large content of diamino acids is much more marked than that of ordinary proteins, such as are found in somatic nucleoproteins. In some species of fishes, the spermatozoon nucleus contains in place of protamine a histone, as the basic substance joined to the nucleic acid. The significant point in this statement is that the histones as a class contain less (about 31–38 per cent.) of their total nitrogen in the form of diamino acids (arginine, lysine and histidine), while the majority of the protamines have 84–89 per cent. of their total nitrogen in this form. Obviously, therefore, the basic portion of the nucleoprotein is subject to decided variation in the sperm of different species of animals, although all are alike in being made up in large measure of diamino acids.

The nucleic acids present in the spermatozoon, as in the nuclei of somatic cells, are composed of a condensed phosphoric acid to which are joined the purine bases adenine and guanine, the pyrimidine derivatives thymine and probably cytosine, with pentose and hexose groups in addition thereto. As expressed by Burian,[13] the two purine bases are joined directly to the phosphorus of the condensed phosphoric acid, so that in all probability a phosphoric acid amide-like combination results. The thymine and cytosine are presumably joined with carbohydrate groups, the latter being in turn bound with the phosphoric acid skeleton after the fashion of an ester. Regarding the cytosine, it is not yet clear whether this substance is a primary component of nucleic acid or a secondary decomposition product of the purine bases. In any event, we have in the sperm nucleic acid a complex substance containing phosphorus in the form of phosphoric acid, nitrogen in the form of purine bases and pyramidine derivatives, together with carbohydrate in the form of pentose and hexose groups. In the sperm nucleus, this acid is combined with a protein, such as protamine, and according to the analyses of Miescher the head of the ripe spermatozoon of the salmon is composed of about 95 per cent. of a neutral salt of salmine nucleate. These are important facts, since they show us something as to the nature of the chemical complex which constitutes the active part of the spermatozoon, and which of necessity plays an important rôle in the synthetical and constructive processes connected with fertilization of the egg and with the later processes of cell division. The dominance of the diamino acids in the protein part of the nucleoprotein (as in salmine) and the corresponding dominance of purine (and pyrimidine) nitrogen in the acid part of the nucleoprotein must impress us as significant when it is remembered that this material is of necessity concerned in the construction of cell, and later, of tissue protoplasm. In making these statements, I have no desire to minimize in any degree the value of other

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[12] *Zeitschrift für physiologischen Chemie*, Band 40, p. 565; Band 41, p. 407, and Band 44, p. 342.

[13] "Chemie der Spermatozoen," II., *Ergebnisse der Physiologie*, Band 5, p. 803, 1906.

lines of work—such, for example, as have been carried on so successfully in this university—notably the influence of changing conditions in temperature, oxygen, proportion and nature of inorganic salts, etc., as determining factors in fertilization and cell division. Still, the striking peculiarities in chemical structure just referred to constantly confront us and call for some logical explanation.

It has been one of the accepted doctrines of physiology in the past that in the animal body the protein of tissue protoplasm is the result of a simple transformation of the food protein; digestion in the gastro-intestinal tract leads to the formation of proteoses and peptones, which after absorption are reconverted into such proteins as are adapted to the needs of individual organs and tissues. Latterly, however, this view has been steadily losing ground. The discovery of the enzyme erepsine in the intestine of man and the higher animals, together with its well-established power of quickly breaking down peptones into crystalline fragments, among which the diamino acids stand out conspicuously, has raised the question whether in the intestine prior to absorption food protein is not more or less completely disintegrated with formation among other fragments, of arginine, lysine and histidine, out of which in the liver or elsewhere specific proteins are manufactured *de novo* to meet the needs of the individual organism. There are many grounds for attaching considerable weight to this view, although the question is by no means settled. The facts, however, point clearly to the probability that in digestion the food protein is more or less broken down into amino acids and very simple peptides, and if the organism is to derive advantage from these nitrogenous fragments for the manufacture of protein to make good tissue waste, then synthesis must be the rule. Further, it is easy to see how by such a method of procedure the animal body is able to construct by a proper selection of these fragments the specific proteins needed by different types or species of organisms; far more easily, indeed, than if the changes undergone by the varying food proteins during digestion are limited to such slight transformations as are involved in peptonization, etc. Assuming this view to be correct, we see a close analogy between the construction of body protein in ordinary nutritive processes and the synthesis of protein in those phases of growth and development associated with fertilization and cell division. In both cases, diamino acids, notably arginine, lysine and histidine, are conspicuous elements, but it is to be noted that in the spermatozoon nucleus the protein part of the nucleoprotein is characterized by great simplicity of structure and with a dominance of diamino acids, notably conspicuous in the protamines, less so in the histones. As constrasted with the proteins of somatic cell nucleoproteins, the difference is very striking and must have some significance. The latter are relatively very complex; a complexity which shows itself in a far larger number of building stones, monoamino acids, etc., with a corresponding diminution in the proportion of diamino acids, such as arginine. We can well conceive that in fertilization and the subsequent nuclear changes which precede rapid cell division there must be some inciting element, some conditions prevailing other than those which characterize the somatic cells, and it would seen justifiable to ask if this peculiar chemical structure of the spermatozoon protein, with its high content of diamino acids, may not be in some measure responsible for the characteristic reactions that accompany and follow fertilization. It is certainly a conspicuous fact that the sperm nucleus of many species of animals contains the same kind of nucleic acid as is found in the nucleoproteins of many somatic cells. Here, there is no noticeable difference in chemical structure, but in the protein part of the nucleoprotein the difference, as has been pointed out, is most striking. Hence, it seems reasonable to suppose that some special function attaches to this peculiar structure of the protein present in the nucleoprotein of the spermatozoon nucleus, although it must be granted that at present there are no facts available to support any theory.

We can not avoid attaching considerable significance to this marked chemical difference in the composition of the cytoplasm and karyoplasm of the sperm cell, any more than we can overlook the striking peculiarity of structure in this particular type of cell, in which the nucleus completely overshadows the cell body. We may well ask why the cytoplasm, composed as it is of a highly complicated mixture of different materials, should be so dominated by a nuclear substance composed almost entirely of a nucleoprotein, the basic portion of which is made up of the simplest type of protein known, with its large percentage of diamino acids? The egg cell, on the other hand, is composed in large measure of cytoplasm, and further, the nucleus of this type of cell has a chemical structure radically different from that of the karyoplasm of the spermatozoon, since such nucleoprotein as it contains is widely variant in chemical make-up from the forms present in the sperm nucleus. It is not strange, therefore, that Miescher and others for a time considered protamine nucleate as the important factor in the process of fertilization. Various lines of experiment have apparently demonstrated, however, that such is not the case; still the problem remains, and there must be some explanation to account for these striking chemical differences in the make-up of the karyoplasm in the two types of cells. The chemist and the cytologist are alike unable to find any adequate explanation for the reactions that occur in the commingling of sperm and germ cells. Extracts of various kinds made from the spermatozoon, which might take up some one or more chemical substances as yet unrecognized, have been so far inoperative in inducing fertilization. There can be no question, however, that many of the problems connected with fertilization, cell division, heredity, etc., are bound up in the chemical constitution of the different components of the sperm and germ cells. Chemical activity of some sort is unquestionably incited by the sperm cell, and we may well believe with Loeb[14] "that the direct and essential effect of the spermatozoon and the methods of artificial parthenogenesis is the starting of a definite chemical process," although we are wholly in the dark as to the exact nature of the reactions involved. It might be conjectured that the spermatozoon serves to introduce a positive catalyzer into the egg cell and thereby starts or accelerates synthetical processes by which the egg is made to develop, with consequent transformation of a portion of the cell protoplasm into the specific nuclein or chromatin substance of the nucleus. Experiment along these lines, however, has failed to give any proof of a positive catalyzer being carried into the egg (Loeb).

There may be legitimate differences of opinion as to the relative importance of the nucleic acid and of the protamine base; of their relative significance in the transference of racial and family characteristics, for example. Loeb, however, has said "that the nucleic acid is of more importance for heredity than protamines and histones." This may be so, although the evidence for such a view is not thoroughly

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[14] "The Dynamics of Living Matter," 1906, p. 178.

convincing. However, this is not the time to enter into detailed discussion regarding such questions, as the chemical evidence is altogether unsatisfactory and fragmentary. We must rest content at present with the few suggestions already put forward, understanding that our object at this moment is merely to emphasize the need of broader and more exact knowledge in a field of investigation where chemical processes are undoubtedly of paramount importance. The problems involved are many, and future advance is to be looked for from chemists as well as from workers in the fields of morphology and cytology.

Students of heredity are inclined to believe, on the basis of Mendel's experiments on hybridization, etc., that each individual characteristic of a species is represented by a definite determinant in the germ cell. As Loeb has expressed it, "this determinant may be a definite chemical compound. The transition or mutation from one form into another is therefore only possible through the addition or disappearance of one or more of the characteristics or determinants." Look where we will and such suggestions as these are ever before us. We may recognize to the fullest degree the value of the work which has been done, and is still being carried forward so successfully, on the chemical dynamics of physiological processes and the important bearing which the results thereby obtained have upon the problems we are now discussing, yet there is still before us the unanswered question what are these specific determinants that are the carriers of heredity? If their individuality is bound up, as may well be believed, in the chemical structure of the protoplasm, what is the nature of the groups involved? What the character of the ions that are instrumental by their presence or absence in determining processes that are so fundamental in the perpetuation of species or in the production of modifications? Biological chemists may well work with enthusiasm on such a subject, and while it may be that one person's thoughts, for example, will lead him to a study of organic structure, another may be led with equal force to investigate the influence of positive and negative electrons on protoplasmic activity, each equally impressed with the value of his work in its possible bearing on the solution of the problem. Indeed, there is, I think, perfect assurance that both lines of work are called for if there is to be found positive answers for the many questions constantly arising relative to the subject of heredity and the transmission of specific characteristics. The problem is indeed intricate, or so appears at present, and we can only hope for success by following up every line of approach that presents itself.

The topics on which I have ventured to touch in this brief presentation are a small fraction only of those which will arise in the minds of most biological chemists in thinking of our present-day problems. The number is indeed legion. Problems of many kinds confront us of varying degrees of importance, and on their solution depends our rate of progress. The spirit of investigation is abroad and it is our duty, as it should be our pleasure, to exhibit all possible zeal in advancing knowledge of bio-chemical processes. Opportunities in this country have greatly increased of late. The time was, and only a few years ago, when it was a rarity to find a laboratory of physiological chemistry attached to a university. Now, such laboratories are to be seen on all sides, and men of power are being trained to carry on investigation in this attractive and promising field of work. Further, the great research institutions recently established, The Carnegie Institution of Washington, The Rockefeller Institute for

Medical Research at New York, various public health laboratories, the laboratories for research connected with many of the more progressive hospitals and asylums of the country, and last, but by no means least, the agricultural experiment stations with their increased funds, all offer opportunities for progressive work which, if properly taken advantage of, promise results of great importance in the development of a more exact and broader knowledge of the chemical processes of life. To the chemist and physiologist there is nothing to be desired more than an increase in the activity of research; research guided by intelligence and knowledge, coupled with an interest which knows no discouragement.

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THE AMERICAN SOCIETY OF VERTEBRATE PALEONTOLOGY

The society held its seventh annual meeting at Yale University, New Haven, Conn., December 25, 26 and 27, the following papers being presented and business enacted.

Dr. G. R. Wieland discussed the extermination of green turtles and whales, showing that while the whaling industry had been prosecuted fully a thousand years, in which time some $272,000,000 worth of oil and bone had been obtained, the total number of whales killed was under one million; but the destruction of this relatively small number is fast exterminating these marine mammals. After an animated discussion the society adopted the following resolution:

> *Resolved,* That the American Society of Vertebrate Paleontologists will aid in every way practicable those measures, legislative, international and local, which will prevent the now immanent destruction of the great marine vertebrates, especially whales, manatees, seals and green or other turtles, on the coasts of the United States and on the high seas.

Dr. F. B. Loomis described a fauna of vertebrates (*Portheus, Ichthyodectes, Saurocephalus, Pachyrhizodus, Empo,* etc.) found in the upper black shales making the divide between the Cheyenne River and Hat Creek, Wyo. This fauna being typical of the Niobrara indicated that the upper beds of the so-called Ft. Pierre of that region are Niobrara, and what is beneath would be Niobrara and Ft. Benton.

Dr. W. J. Sinclair showed that the material of the Washakie was practically all volcanic ash, probably distributed by wind and streams.

Dr. G. F. Eaton discussed the skull of *Pteranodon,* showing that the basal portion was peculiar in the development of the parasphenoid, and unique in the possession of diagonal rods running from the base of the parasphenoid to the transpalatines. The origin of the crest was partly attributed to the great development of grasping muscles (connected with the supposed piscatorial habit of feeding) and was compared with incipient crests in the fish eating birds *Plotus* and *Phalocrocorax.* The striking similarity of the pelvis to that of birds was pointed out.

Professor Joseph Barrell read a paper in which evidence was given showing the widespread development of flood plain deposits in the Old Red Sandstones basins and the presence of a fluviatile piscine fauna. The climate was genial and subject to recurrent seasons of dryness. The footprints of the earlier amphibia often show also an association with fluviatile deposits and an adaptation to even semiarid climates. In the discussion of various factors tending to bring about the evolution of the Amphibia the influence of recurrent seasons of dryness upon a fluviatile fauna appeared to be by far the most