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TWENTY-FIVE YEARS OF BIOCHEMISTRY[1]

TWENTY-FIVE years ago I gave my last lecture in America as an instructor in chemistry in Harvard University, after two years of industrial and two years of academic work in this country. I did not then expect ever again to address an American audience, and even less did I anticipate the honor of being allowed to report in this great university about the special work to which I have devoted all my interest and energy during the last two and a half decades. I wish therefore first of all to express my sincere thanks to Professor Dennis and Cornell University for the invitation which affords me this opportunity.

As an introduction, it would seem best to attempt a short historical review of the branch of science that is generally termed "biochemistry." Because of the limited scope of this lecture I will define biochemistry in a somewhat arbitrary manner, as the chemistry of physiologically important organic substances which are essential to the living organism of animals or plants.

Biochemistry as a special branch of study or as a particular field of instruction is of quite recent origin, and a history of biochemistry has not yet been written. In the brief time at my disposal this evening it would be quite impossible adequately to review the progress in this branch during the last quarter of a century, and I will therefore attempt merely to outline the chief developments in this field. Detailed discussions of the progress may be found in the writings of that important contributor to biochemical literature, Oppenheimer.

In earlier times when experimental chemistry was exclusively in the hands of physicians and pharmacists, who by the nature of their work should especially have been interested in biochemistry, very little progress was made. The reason for this lies in the fact that important biochemical substances were very complex, a characteristic which renders their investigation difficult. Before entering upon the study of such substances it was necessary that precise knowledge of inorganic substances and reactions should first be gained, and the successful investigation of these bodies naturally had to be preceded by adequate

[1] Introductory public lecture by Professor Hans Pringsheim, of the University of Berlin, non-resident lecturer in chemistry at Cornell University.

development of organic chemistry, the one hundredth birthday of which we are celebrating this year. The earlier investigators rarely studied material of biological origin and only the great leaders in the science had the courage to enter upon this field. If we except the fundamental work of Chevreul on the constitution of the fats, which are in many ways the simplest biological compounds, the investigations of that period must, from the present-day standpoint, be regarded as preparatory only. One biochemical process, however, that of alcoholic fermentation, early attracted the interest of chemists. In the first half of the last century Gay-Lussac studied the question of the decomposition of sugar by yeast, and Pasteur and Liebig entered into their celebrated controversy concerning the causes of this decomposition. To Eduard Buchner we are indebted for the discovery that the enzyme which catalyzes the decomposition of sugar into alcohol and carbonic acid may be separated from the cell of the living yeasts. Emil Fischer devoted most of his attention to substances of biological origin. Most of his researches on sugars and purines preceded the period of which I am speaking, but his investigations on proteins and tannins belong to it.

Twenty-five years ago there existed only one journal devoted to the subject of biochemistry, the *Zeitschrift für physiologische Chemie,* which Hoppe-Seyler founded in 1877. About twenty-two years ago the *Biochemische Zeitschrift* first appeared in Germany, the *Biochemical Journal* in England and the *Journal of Biological Chemistry* in this country. In 1922 the Japanese *Journal of Biochemistry* was started. Interest in this field has so rapidly developed that the reports of investigations in biochemistry fill not merely the journals which I have just mentioned but form substantial parts of the reports of the meetings of the various chemical societies. New chairs of biochemistry are being endowed, new laboratories with special equipment are being constructed in various universities and institutes devoted exclusively to research, such as the Rockefeller Institute for Medical Research in New York City, the Rockefeller Foundation in Stockholm and the Kaiser Wilhelm Institute in Germany. We thus see that biochemistry is attaining equal rank and equal recognition with inorganic, organic and physical chemistry.

We can, perhaps, best follow the development of biochemistry by considering separately the three groups of substances that are most essential to the living cell, namely, the fats, the sugars and the proteins. In this discussion I shall have occasion to refer to other substances more or less directly connected with these bodies.

THE FATS

The fats, which are the principal reserve substances of the body, are esters of glycerol with long-chain fatty acids. A large part of the necessary living energy is supplied by their oxidation. Now such compounds as the fatty acids of the paraffin series are very resistant, and it is difficult to explain how their oxidation could take place under the mild conditions of cellular life. It was, therefore, a great achievement when Knoop and others showed that the oxidizing forces attack by preference the second carbon atom from the carboxyl group (the beta carbon atom) so that step by step two carbons are always split off until finally the whole chain is broken down into water and carbon dioxide.

Closely related to the fats are the lipoids which contain, in addition to the fatty group, phosphoric acid and a basic substance in the molecule. The lipoids form part of every living cell and are of primary importance in the regulation of the passage of food substances through the cell members. Levene, of the Rockefeller Institute in New York, has made a special study of the phosphatides and was the first to prepare a really pure lecithin. His work on the related cephalin of the brain is also noteworthy.

Fats are insoluble in water and in the normal medium of the digestive tract. For their transportation and digestion they must be distributed so as to expose a large surface and this is arrived at by emulsion. The bile secretes a juice which passes into the intestines and has a special power to dissolve the fats. The principal organic substances of the bile are the so-called bile acids, hydroaromatic compounds of complicated structures, which have been the subject of the investigations of Wieland, Schenk, Borsche and others. It is interesting to note that cholesterol, which also forms part of the bile, and is accumulated in the bile stones, is, according to Windaus, constitutionally closely related to the bile acids. One of the most important results of biochemical research is the discovery by Windaus in Germany, Rosenheim in England and Hess in America that ergosterol, a compound belonging to the cholesterol group, under the influence of ultra-violet rays, is transformed into an accessory food substance or vitamin. A new and important field of biochemical work and one of great promise from the medical aspect has been opened up by these investigations.

THE SUGARS

The sugars form another group of important biochemical substances. They are made up of carbon, hydrogen and oxygen. Emil Fischer has made clear the structure of the simple sugars, such as glucose, fructose, mannose and others, through his classical investigations, and he determined their structural configuration on the basis of the stereochemical laws which had then just been enunciated by LeBel and van't Hoff. Fischer succeeded in synthesizing the above monosaccharides and studied their behavior toward enzymes. One of his greatest achievements was the discovery of the specific qualities of these biochemical catalysts, an observation that has been of outstanding importance in the development of this branch of biochemistry. Many scientists have contributed to our knowledge of sugar chemistry, among them being Kiliani, Lobry de Bruyn, Bertrand and Bourquelot. Tanret prepared for the first time the two stereochemical forms of glucose which we now call alpha glucose and beta glucose.

In the early part of the twentieth century Emil Fischer devoted himself to the tannins, a class of substances chemically derived from the sugar molecule by substitution with the residues of gallic acid. This work was continued and developed chiefly by his pupil Freudenberg.

After his early work on the sugars Fischer discontinued for a time his investigations in this field, but during the last years of his life he again took up the study of these bodies and discovered a number of important changes in the glucose molecule, which were developed by his coworker, Bergmann, and which inaugurated a new period in sugar chemistry. We are still living in this era; it has spread over the whole world, and it is not an exaggeration to say that there is now appearing in chemical journals about one article a day that has some bearing on the chemistry or biochemistry of the carbohydrates.

A new impulse was given by the discovery by Hudson, of the Bureau of Standards in Washington, of certain rules, based upon the additive quality of the rotatory power, which relate the optical rotations of the sugars and their derivatives under mathematical rules. Hudson and also Levene have demonstrated the validity of these rules which in many cases enable us to predict the specific rotation of unknown sugars, and to draw conclusions from the rotatory power concerning the constitution and configuration of simple and complex carbohydrates.

In the field of the disaccharides and the trisaccharides the recent advance is quite remarkable. The constitution of such disaccharides as maltose, lactose, cellobiose, gentiobiose and others has been cleared up by the methylation process, which for many years was investigated by Purdie and Irvine, of St. Andrews University, and which has lately enabled Irvine and Haworth to make a definite formulation of the constitution of these substances. Their conclusions were later confirmed by Zemplén, of Budapest, who used a different method. It was discovered that cane-sugar contains, in its fructose portion, a special form of an unstable sugar molecule, a gamma sugar, which after inversion changes into the stable form. Such unstable sugars are formed preferentially as intermediate products in the natural assimilation processes of plants and animals, in the metabolism of starch, glycogen and inulin.

One of the chief aims of the chemist, the synthesis of some of the polysaccharides of established constitution, has now been attained. Gentiobiose has been synthesized by Helferich, and maltose and lactose by Pictet, the great Swiss chemist, who has recently solved a problem of great difficulty, the synthesis of cane-sugar.

But the ambition of sugar chemists goes still further. They hope to ascertain the complicated structure of the complex polysaccharides which are formed by nature in the colloidal state. Whereas only ten years ago one hardly ventured to discuss the constitution of such substances as starch and cellulose, many are now occupied with the investigation of the chemistry of these bodies. These colloids belong to a class of compounds which are characterized by "large molecules," and they display unusual properties which will have to be studied by new methods and with new chemical conceptions for their explanations. It is also quite recently that we have begun to see light in this field which was formerly so obscure. The opinions in regard to the general chemical behavior of these bodies are quite contradictory as is frequently the case in a new branch of scientific research. A new definition of the term "molecule" or a substitute for it must be found for these complex substances of high molecular weight. The organic chemist usually studies substances that are in the gaseous state or in solution, but here we have to deal with bodies in the solid state. New physical methods must be employed, one of the most promising being the employment of X-ray diagrams which have given us such an insight into the crystalline state of matter. But even along this line the conclusions are not as yet definite. Colloid chemistry has been of aid in the explanation of the behavior of the complex polysaccharides, but the investigators in this branch of science, which has attained great importance during the last decade, are still so occupied in studying the laws which govern simple inorganic colloids, that they have only in exceptional cases concerned themselves with organic compounds. The colloidal studies of Samec on starch are therefore of particular biochemical importance. The history of the chemical investigations of starch has recently appeared in a very attractive book from the New York Public Library; it contains the complete literature of the subject and gives the present state of the chemistry of the starches as developed by the work of Pictet, Irvine, Karrer, Kuhn, von Euler, Sjöberg, Ling, Sherman and others.

The polysaccharide, cellulose, is at present attracting the greatest interest throughout the world, largely because of its dominating importance in the manufacture of paper and artificial silk. Cotton, which is produced in tremendous quantities in this country, is nearly pure cellulose, but almost all of this is used in the manufacture of cloth. The cellulose that is used in the industries is obtained from wood and the chemistry of this process during recent years has been developed with great success by Klason, Schwalbe and Heuser, by Schorger and Wise, Erich Schmidt and Hägglund. Special laboratories for the study of cellulose and wood have been established in the United States and in Europe, and one in Toronto, of which Hibbert is the director, is just being completed. Special credit should be given to Herzog for the introduction of X-ray methods in the study of cellulose and related substances. These investigations as well as those of Katz, Mark and Sponsler, combined with the chemical studies of Hess, Bergmann, Freudenberg, Irvine and other chemists throughout the world have contributed greatly to a clearer conception of the physical and chemical properties of this most important skeleton substance of plants. In addition to this study of the biologically interesting carbohydrates the investigation of their transmutation by the cell and its enzymes has been greatly advanced during recent years. The finer phases of the decomposition of sugars by alcoholic ferment have been carefully investigated by Harden and Neuberg, who discovered special desmolytic enzymes and cleared up the intermediary stages of alcoholic fermentation as well as numerous bacterial fermentations. It has been shown that the manner in which these bodies are broken down by lower organisms is very closely related to the decomposition of the substances in the animal body, especially in the muscles. To Hill, Meyerhof and Embden is due new insight into the muscular enzymes and into the relationship which exists between the lactic acid and glycogen equilibrium in muscular contraction. Warburg has combined physicochemical methods with biological ones with great success and has ascertained that biological oxidation is related to the iron content of the cell, which he considers to be the essential oxidizing catalyst. On the other hand, Wieland has brought forward the theory that biological oxidation depends upon the activation of hydrogen and not of oxygen atoms. Both theories are supported by very valuable and original experimental work.

The study of the enzymes which split the carbohydrates was made the basis of a most important series of investigations upon enzymes in general by Willstätter and von Euler, who prepared them in a state of purity far surpassing that of earlier products. These new methods for the purification of the biological catalysts were based principally upon their behavior as colloids, and have been applied with equal success to the enzymes which act upon fats, proteins and other substrates. These epoch-making researches of Willstätter were presented by him in April of last year to a Cornell audience in his lectures on "Problems and Methods in Enzyme Research" which he delivered in this room.

Sugars also form a part of the molecule of the pigments which make roses, geraniums, blueberries and other plants attractive to the eye. Willstätter has also cleared up the constitution of these anthocyanins and has shown that they belong to the same chemical group. He has also, with wonderful experimental skill, given us a clearer understanding of the complex molecule which gives the green color to leaves and that is the agent by means of which light energy reduces the carbon dioxide of the air. He has shown that the molecule of chlorophyll is held together by the metallic element magnesium and that magnesium gives to it its reactive properties. Iron plays the same rôle in relation to the red color of the blood. Here again we find that nature forms its most important reagents in closely related chemical structures, since the color of leaves and of blood is due to similar cyclic groups. Willstätter, Piloty, Küster, Schumm, Hans Fischer and others have greatly advanced our knowledge of the constitution of the blood pigment. Their work has enabled Hans Fischer to come close to building it up through his most remarkable syntheses.

We can not leave the field of sugar chemistry without speaking of the discovery of insulin, the hormone of the pancreas which is so essential to the oxidation of sugar in the animal body. The benefit of this great achievement which was accomplished on this continent is enormous, not only in the treatment of diabetes but also as a stimulus to the study of hormones in general, a group of bodies which Professor Barger described in his lectures in this laboratory last term.

THE PROTEINS

The proteins differ in elementary composition from fats and sugars in that they contain nitrogen, and they have always been considered a particularly complicated problem for the chemist. The great variety of changes which they undergo makes it difficult to extract and characterize them. Consequently the earlier investigators in this field in the nineteenth century devoted their energy chiefly to the purification and classification of the various albuminous substances of animal and plant origin. Only a few of the amino-acids which build up the protein molecule were known in about the year 1900 when Emil Fischer devised new methods for their separation. At about the same time Kossel made a special study of the protamines, a comparatively simple group of proteins which occur in fish eggs, and he discovered how the more complicated amino-acids in them might be separated. Abderhalden in Germany and Osborne in America extended our knowledge of the composition of proteins and Felix Ehrlich discovered a new amino-acid, isoleucine. Ehrlich showed further how fusel oil, the by-product of alcoholic fermentation, is formed by the decomposition of amino-acids. Dakin has recently discovered the nineteenth of the amino-acid constituents of proteins.

Emil Fischer conceived that the amino-acids are combined in long chains in the protein molecule and this led him to attempt a synthesis of protein-like substances termed polypeptides. These bodies resemble in many respects the peptones, the higher degradation products of the proteins, and several of them were found in the hydrolytic products of casein, gelatine and other proteins. The dipeptide, glutathione, which consists of cystine and glutaminic acid, was discovered by Hopkins in most cells. He regards it as playing an important rôle as an acceptor for hydrogen which results in the liberation of oxygen for oxidation processes. The most important characteristic of the synthetic polypeptides of Emil Fischer is that they are hydrolyzed by specific proteolytic enzymes of the digestive tract.

During about the same period our understanding of the metabolism of proteins was very considerably developed. It was shown by Abderhalden that the proteins might be substituted by a mixture of the amino-acids which resulted from the hydrolysis, but only glycocoll can easily be formed from other amino-acids. The others must be present in the food to guarantee the nitrogen equilibrium, without which cell life can exist only a short time. Gelatine, which lacks two amino-acids, trypthophane and tyrosine, can be made a complete protein from the standpoint of nutrition by adding the two amino-acids derived from other sources.

Here again, as in the case of sugar chemistry, a new impetus was given to investigation after the close of the World War. This impetus resulted from the hypothesis that the protein molecule does not consist of peptide chains of great length as Emil Fischer had supposed. In analogy to the new conception that complex polysaccharides are aggregates of small molecular building stones, the suggestion was brought forward that in proteins a similar arrangement should be possible. This theory found some support in X-ray studies which showed a crystalline structure for substances related to a dipeptide anhydride. By rather vigorous reactions, which did not exclude rearrangement, compounds of ring structure were obtained from the proteins. We now know that these views were for the greater part premature, but they have stimulated experimental investigations in a most beneficial manner. A finer analysis of the hydrolytic cleavage of proteins by methods devised by Sörensen, Van Slyke and Willstätter has helped us greatly to reach sounder conclusions.

The greatest progress in protein chemistry has resulted from the application of their specific enzymes. Marked advances in enzyme chemistry have resulted from the observations of Sörensen of Denmark and Michaelis of the Johns Hopkins University, that the hydrogen-ion concentration of the medium must be determined with great exactness. The methods for ascertaining hydrogen-ion concentration and for keeping it constant by the addition of buffer solutions made it possible to determine the optimum acidity point that is a characteristic constant for each enzyme. But the greatest advance in the biochemistry of albuminoids was the first actual separation of the proteolytic enzymes by Willstätter and his coworkers, especially Waldschmidt-Leitz. The pepsin of the stomach can easily be obtained in a state of enzymatic purity, but what had previously been considered to be pure trypsin was shown to be a mixture of that body with erepsin, which was discovered twenty-six years ago by Cohnheim in the intestines. By adsorption methods, trypsin and erepsin were separated and they may now be considered as analytic biological reagents. It had earlier been known that the pancreatic enzyme was accompanied by an activator, enterokinase, but only after their separation had been accomplished was it possible to show that trypsin is an enzyme of quite specific properties, and that it changes into another equally characteristic enzyme after the activator is added to it. Similar results were obtained with the plant enzyme papain, which is activated by hydrocyanic acid. The purification of the proteolytic enzymes such as those of the yeast cell shows that there are several enzymes which exert their optimum activity on substrates of varying structures and of graduated molecular complexity. So here again, as in the case of polysaccharide chemistry, the enzymatic reactions are of great value not only in distinguishing different protein-like substances but also in enabling us to draw conclusions regarding certain groupings of the amino-acids in the protein molecule. This work which is now being carried on by Waldschmidt-Leitz and other pupils of Willstätter gives promise of great success in this complicated field. The fact that pepsin causes true hydrolytic decomposition and not merely a physical degradation, and that the diketopiperazines, cyclic structures derived from amino-acids, are not attacked by proteolytic enzymes, brings us back to the old conception of the protein molecule consisting of great polypeptide chains. The number of possible linkages by which they might be united is enormous, and we can now only hope for the development of a general theory and not for a detailed knowledge of the structure of the proteins. The study of their colloidal behavior which was inaugurated by Jacques Loeb in this country promises to be of great value in the further development of biochemical research.

From birth to death the life of man is dependent upon biochemical reactions. They take part in the supply and preparation of his food and aid him in its digestion. Cooking and baking, preserving fruit and salting meat, the making of cheese and sour milk, all involve biochemical changes. The process of retting flax and hemp, which are so essential for our clothing, the fermentation of tobacco, which contributes so greatly to the happiness of many, are biochemical reactions. Fermentation processes are involved in the preparation of natural fertilizers, without which an intensive form of agriculture is impossible. Most of the problems of agriculture which have been studied with such great success in the various experimental stations in this country are directly related to biochemistry. The connection between the formation of humus in the soil and the decomposition of its content of micro-organisms, as investigated by Waksman in New Brunswick, is of great interest.

Biochemical principles underlie the purification of our water supply and the destruction of refuse. They enter very largely into the field of medicine and furnish us with many methods for the curing of disease. But great as is their importance, our knowledge in this field is small.

The biochemical reactions of the life processes are extremely complex, and as yet we understand only vaguely the general laws which govern them. We have ascertained many separate and apparently unrelated facts, but we are still unable to make predictions that are based upon mathematical laws. At the present time physical science seems to offer greater attractions to the investigator because of the opportunities that it affords for study of the basic laws of the phenomena of nature.

Nobody can nowadays achieve any great discovery in biochemistry through purely theoretical deduction; important advances can be obtained solely by exhaustive experimental research. And only those heroes of our science who are willing to withdraw their minds from most other interests of human life can hope to accomplish really great results.

Every young student who cherishes the hope of being able at some future time to make a worthy contribution to our knowledge of biochemistry, whether it be of theoretical or practical importance, will have to choose one of two courses that are open to him. He may, and most probably will, follow the general line of development and become a useful but routine chemist, or he may, imbued with higher aspiration, enter upon a road of his own into the dark wilderness of research. His path at the beginning may be strewn with thorns, he may meet with disappointment and discouragement, but in the end he may pick from the tree of knowledge a fruit that is far sweeter than any that he may otherwise have tasted. Let us hope that many of the younger scientists in this audience may be carried forward by their enthusiasm along this road.

Hans Pringsheim

Ithaca, N. Y.

THE THIRTEENTH INTERNATIONAL PHYSIOLOGICAL CONGRESS

The Thirteenth International Physiological Congress is to be held at the Harvard Medical School in Boston, August 19 to 23, 1929. This, the first meeting of this body to be held in America, promises to be of great interest to American physiologists. It comes just forty years after the first congress met in Basel in 1889. In that the tradition of these congresses was in large part determined by a letter sent out from the office of the Physiological Society in London, as a result of which the first congress convened, it seems appropriate to reprint that letter at this time.

Physiological Society, London.
19th March, 1888.

Sir,

It is suggested that International Meetings of Physiologists should be held at intervals, with the object of promoting the progress of Physiology by the interchange of ideas and mutual friendly criticism, and of affording opportunities to workers in our science of knowing each other personally.

It is proposed to include in the subjects to be brought before such a Meeting only those branches of Anatomy, Histology, Physics and Chemistry which directly bear upon Physiology. With the ample opportunities already existing for the publication of Physiological Papers, it appears unnecessary to provide for printing separately the Transactions of the Meetings. It is intended that all