SCIENCE

VOL. 74 FRIDAY, JULY 10, 1931 No. 1906

SCIENCE: A Weekly Journal devoted to the Advancement of Science, edited by J. MCKEEN CATTELL and published every Friday by

THE SCIENCE PRESS

New York City: Grand Central Terminal

Lancaster, Pa. Garrison, N. Y.

Annual Subscription, $6.00 Single Copies, 15 Cts.

SCIENCE is the official organ of the American Association for the Advancement of Science. Information regarding membership in the Association may be secured from the office of the permanent secretary, in the Smithsonian Institution Building, Washington, D. C.

THE REVOLT OF THE BIOCHEMISTS[1]

By Dr. P. A. LEVENE

THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH, NEW YORK

MAY I begin my remarks of this evening by acknowledging my gratitude to the men to whom I owe the great honor of having my name added to the truly illustrious names of the Willard Gibbs medalists who have preceded me. I am referring to the Board of Scientific Directors of the Rockefeller Institute for having liberally supported the work of the Chemical Division and to Dr. Simon Flexner for his help and encouragement, and then to those who have participated in the work of the Biochemical Division of the Rockefeller Institute, some for a longer and some for a shorter period of the twenty-seven years of the existence of the chemical laboratories.

To your section of the American Chemical Society and to the committee of award, I owe a special debt of gratitude, for I accept the medal not as a personal tribute but as an expression of recognition of that branch of science to the progress of which we have devoted our energies.

To-day, this branch of science is in need of encouragement. Even in European countries where biochemistry has had a long and glorious record and a great tradition, it is held somewhat in disfavor today. The story of the rise and fall of biochemistry in the esteem of the higher scientific hierarchies is in a way connected with the incident of the revolt of biochemistry against the concept of vital force or, as the Germans call it, "Lebenskraft." This was a revolt against restriction of the exploits of the human mind, for, modest as the domain of biochemistry may be, it had to align itself with some more universal philosophy in order that it might remain in the family of sciences.

Until nearly the middle of last century, every chemist was a biochemist. Chemical hierarchies did not yet exist. All natural substances whether of mineral,

[1] Address on the occasion of the acceptance of the Willard Gibbs medal.

vegetable or animal origin were included in the scope of interest of every chemist. Chemistry was a purely descriptive science. Substances were the subjects not only of curiosity but also of affection. Theory, whatever there was of it, played a subordinate part in the life of the chemical investigator. His mental attitude was that of a collector of "rarities." Indeed, how else could one understand the reactions of a man of the type of Scheele? In a critical period of his life a position was offered to him as head of an apothecary shop in a small town, Koping, in Sweden. An inferior competitor snatched the job from him; whereupon his friends in his native land, as well as in other countries, set out to secure a more advantageous post for Scheele. Offers came from Berlin, from England and from Upsala. And what was Scheele's reply?—"I can not eat more than my appetite permits and if I can find enough bread in Koping, is there any need for me to search for it elsewhere?" The life of Scheele was truly serene. He owed comparatively little to the theoretical legacy of the past and had no obligation to the generations to come.

Scheele, himself, however, made the task of the generation which followed him more difficult, for he did something which contained the seeds of a new era. In the year 1777, Bergmann wrote that organic synthesis was beyond any hope of success, but in the year 1782–1783 Scheele prepared potassium cyanide by fusion of graphite, potash and salammoniac (NH_3HCl) and thus truly was the first to prepare synthetically a substance containing the element carbon linked to nitrogen and thereby to accomplish the first organic synthesis. But the significance of the achievement was not recognized at the time. Indeed, Fourcroy, in his famous text-book which appeared over 20 years after Scheele's death, maintained that whereas minerals are the products of ordinary physical forces, organic substances owe their origin to a force of an entirely different category, namely, to an organic vital force. Whereas the first were common natural forces, the latter were characterized by purposiveness. This definition does not sound much different from the one advanced by the modern Neovitalists.

Not Fourcroy alone but all great chemists of the early part of the last century were orthodox believers in the doctrine of vital force. Thus Berzelius believed that the secret of the origin of organic compounds lay not in the elements which entered into their composition, not in the element carbon, but in the fact that they were produced by an organism, or rather by organs of a living organism, and the term "organic" was meant to emphasize their origin. In the year 1827, Berzelius was still of the belief that the organic compounds could never be synthesized in the laboratory. Yet only a year later his own student, Wöhler, accomplished the synthesis of urea. "Did this reaction mean a transformation of inorganic material into an organic substance?" was the question which he asked of his old master, Berzelius. The answer was polite but non-committal.

To us to-day, the year 1828 stands for the date of the great revolt of the biochemists against the "Lebenskraft," or the "Spiritus Vitae." In reality, the true revolt came much later. Tradition is too comfortable an armor to be cast off at the first assault. Berzelius continued to refer to the synthetic substances as "incomplete imitations of the organic products." Gerhardt, one of the most brilliant theoretical chemists of the middle of last century, in 1842 maintained that the vital and the chemical forces are of antagonistic nature, the former accomplishing the synthetic functions and the latter that of degradation. Under normal conditions of life, the two forces are balanced; after death, the chemical forces of disintegration are unchecked.

Finally, doubts crept into the minds of some of the chemists. Thus, we find Liebig was ready to make concessions to the new tendencies. He wrote, "Under the influence of a non-chemical agent (Life, Vital Force) chemical forces also function in the organism. Through the guidance of this dominant force and not independently, elements arrange themselves into chemical substances such as urea in the manner in which the intelligent will of the chemists forces them to unite outside the organism. Hence, it will be possible to prepare in the laboratory quinine, caffeine, plant pigments and dyes but not a cell, muscle fiber, or a nerve fiber." Mulder, another biochemist of lesser magnitude as a contributor, but an able thinker, writing on "Organic Forces" states that the assumption of the existence of a peculiar vital force (Lebenskraft) was not supported by experience and furthermore he defends the thesis that the organic forces of the complex substances pre-existed potentially in the elements composing them.

All these utterances, however, were peaceful philosophical speculations lacking the momentum necessary to produce a real revolt against the authority of the vital force. Finally, the revolt broke out effectively in 1860, when Berthelot wrote, "The objective of our science is to banish 'Life' from the theories of organic chemistry." The successes in organic synthesis were behind the authority and the power of this utterance.

The end of last century continued vibrating with the enthusiasm contained in the words of Berthelot. The hopes and expectations of chemists then knew no bounds. Not organic substances alone but organized living matter seemed within reach of the synthetic method. The chemist was not isolated in his hopes and expectations. Physiologist, general biologist, physicist, psychologist and metaphysician were all under the same spell of mechanistic philosophy.

The strides made by organic synthesis for a time surpassed all expectations. It suffices to read the public utterances of Emil Fischer, perhaps the most daring chemical virtuoso and at the same time the most cautious man with respect to theory or prediction, in order to realize the depth of his conviction that organic synthesis would penetrate into and would reveal the mysteries of living matter, if not of Life itself. Indeed, in one of our conversations, he expressed belief in the possibility of synthesizing enzymes.

But as our century advanced, a change came in the general attitude of men of science. Mechanistic philosophy fell into disrepute and with it biochemistry, as one of the foundation stones of mechanistic biology, lost its prestige. Vitalism again came to the front, under the name "Neovitalism." The truth is that the "Neo" philosophies divorce the inorganic forces from the organic as much as the old vitalistic philosophy had done. The monism of the mechanistic philosophy is banished and the "Lebenskraft" is reinstated.

Shall this state of mind of the philosophies of our day alter the attitude of biochemistry? Shall chance, probability, indeterminism become the foundation of the philosophy of biology as they are of the philosophy of the physical world? Shall life forever remain a word without an accurate definition? The retreat is cut off for the biochemists as it was for the revolting angels of Anatole France.

True, for the individual worker, there is some justification for having moments of depression. The achievements of biochemistry may seem disproportionate to the effort, when one thinks of the time it took to unravel the structure of one substance alone. Uric acid was one of the first biological substances to have interested seriously the biochemist. It was discovered independently by Bergmann and by Scheele in 1776; yet only in 1898 was the knowledge of its architecture fully attained by Emil Fischer. Hemoglobin has a similar history. It was in the year 1849 that a biologist saw, under the microscope, its beautiful crystals, but not until 1929 was the architecture of hemin unraveled by Hans Fischer, while the entire structure of the crystals seen by Leyden in 1849 is not yet known. Still more discouraging is the history of proteins. These substances were known since the earliest times. In 1860 the term "protein" was introduced by Mulder, who already at that time speculated on their structure. Yet how little do we know about the details of the structure of a single protein; and the number of them in nature is endless. Think of the chromatins, which are supposed to be the carriers of heredity and of reproduction! They were discovered in 1869 by a very able biochemist, Miescher, who, in his turn, was inspired by a biologist, His, and the structure of the substances is not yet known in every detail. Again, it is discouraging to think of the inadequacy of our information about the structure of starch, cellulose, gums and similar substances. Even in regard to glucose, a substance of very simple composition, and a most common component of our daily diet, the knowledge of the details of its structure is not yet complete, though the substance was obtained in pure crystalline form in 1660 by Glauber.

The science as a whole, however, taking stock for the period of one hundred years, will find a record of achievement which once seemed unattainable. It is enough to compare the humble attitude of Liebig and Wöhler with the daring of Fischer. Having made the discovery that urea constituted a part of the molecule of uric acid, Liebig and Wöhler concluded that uric acid is a complex of urea with a *second radicle* the nature of which in all probability would never be revealed. And yet they had in their hands enough data to permit the formulation of the molecular architecture of the substance, had chemical theory been advanced to its present state. And indeed, Fischer, having accomplished the task which Liebig and Wöhler thought unattainable, attributed his success not to any special individual merit but to advances in theory and in the technique of organic chemistry of his day. To-day, it may be taken for granted that the discovery of the structure of every natural organic substance is only a matter of time and organization. The tools for this aim are in our hands. New achievements in this direction no longer will contain the element of surprise and it is not expected that they will reveal deeper secrets of the mystery of Life than those already in our possession.

Had biochemistry discovered no new ways, no new methods for attaining the aim formulated by Berthelot, namely, to banish Vital Force from chemical theory, then the "Neovitalist" might have been justified in his pessimism in spite of the past achievements of synthetic biochemistry. However, biochemistry to-day has opened new avenues of approach towards its goal. If the interest of the biochemist of the past was structure, that is, the static state of the molecule, the interest of the biochemist of to-day is the functional side of the molecule. It may be remarked that this approach is not entirely new; but in the past it stood in the background, whereas to-day it is the dominant concern of our branch of science. True, as soon as inorganic catalysts were discovered, Berzelius advanced the idea that life phenomena are the resultant of the play of catalysts, though of a different category from that of the mineral catalysts. In the present-day terminology they would be referred to as "biocatalysts." Berzelius believed that every living organism, plant or animal, contained an infinite number of these catalysts.

In the days of Berzelius, of Wöhler and of Liebig, the nature of the biocatalysts was as great a mystery as that of *Life* itself and the quest into their chemical nature held out so very little promise of success that it was tacitly forbidden. To-day, the chemical nature of at least some enzymes is no longer a matter of mystery, and much unexpected information has been obtained regarding the mode of their action. It is known to-day that the action previously attributed to a single agent, a single biocatalyst, is in reality the product of the combined action of a group of agents. Biocatalysts, or enzymes, as they are often called, are characterized by their instability, particularly with regard to heat, and these very unstable components, playing an important part in all life phenomena, are often powerless to act in the absence of definite accessory agents which are known under different names, as coenzymes, complements, activators or kinases. The chemical nature of these last substances is one of the foremost problems of to-day. Many of them have been isolated and have been found to be fragments of the more complex substances, being, for example, simple peptides which are fragments of proteins, or simple nucleotides which are fragments of nucleic acids, while others have been found to be of still simpler composition. These simple substances do not play the part of accessories only, but in some instances exercise a directive influence, causing one and the same enzyme to function in one of several possible directions. It may suffice in this place to refer to the lipases, the fat-splitting enzymes, which were made to produce dextrorotatory or levorotatory acids depending upon the choice of inert substances added to the reaction mixture. These discoveries are very significant inasmuch as eventually they may lead to a revision of our views on the great multiplicity of the biocatalysts.

The mechanism of the action of the accessory substances is not the same in every instance. They may activate either the enzyme or the substrate or both in order to bring about a coupling between substrate and enzyme. In the cases of fermentation and animal combustion of sugar such an alteration of the substrate (sugar) is generally accepted and certain information regarding the structure of the altered fermentable sugar already is available. Thus, again, new problems are created, those of the chemical differences between the stable molecules which were the concern of the older biochemists and the unstable molecules which are the concern of the newer biochemists. The change in stability of certain substances can be produced now by chemical means. The grape sugar molecule seems to be activated by introducing certain groups such as phosphoric acid in a definite position of the molecule. The stability of the smaller fragments of the protein molecule can be lowered by attaching certain acidic groups to the peptide nitrogen and one exceptionally stable component of nucleic acids is made very labile by hydrogenating one of its parts. By selecting suitable media, the chemist has learned to direct a reaction in a desired sense when two substances may interreact in several different ways. And so one of the most characteristic peculiarities of living matter, the directive force, has been imitated in the laboratory. It is not important that as yet this phase of our knowledge is limited. The significant thing is the formulation of the problem. Its solution is a matter of routine, a matter of the ordinary ingenuity of the human mind.

Granting that the problem of the directive force will be solved, it may also be granted that the entire mystery of life will not be solved by this achievement. Chemistry, however, is already preparing a new attack. A more essential characteristic of living matter than the directive force of individual chemical reactions is the power to coordinate all chemical reactions in such a way that the organism may function as a whole for the purpose of maintaining its normal equilibrium and for the purpose of growth and reproduction. This may be regarded as the integrating force of the living organism. The discoveries of the last decade alone furnish proof of the simplicity of the agents acting towards this end. Think of all the hormones and vitamins! Only those which as yet have not been isolated may be thought of as complex and mysterious. Those obtained in pure state are most generally found to be much simpler in chemical structure than many of the ordinary tissue components and definitely simpler than certain common drugs. In fact, many of them are nothing more than degradation products of common tissue constituents. Thus, it seems that in the living organism the very wear and tear of the living matter makes for its restitution and for its preservation. A decade is only an infinitesimal interval in the life of mankind and without hesitation or doubt, one may predict that the nature of all hormones and vitamins and other biologically important integrating substances will eventually be discovered.

Thus, step by step, one mystery of life after another is being revealed. Whether the human mind will ever attain complete and absolute knowledge of and complete mastery of life is not essential. It is certain, however, that the revolt of the biochemist against the idea of a restriction to human curiosity will continue. Biochemistry will continue to function as if all knowledge, even that of life, were accessible to human understanding. The past has taught that the solution of one problem always opens up a new one. New discoveries in physics, in mathematics, in theoretical chemistry furnish new tools to biochemistry, new tools for the solution of old problems and for the creation of new ones. So long as Life continues, the human mind will create mysteries and biochemistry will play a part in their solution.

CLINICAL INVESTIGATION[1]

By Dr. FRANCIS G. BLAKE
YALE UNIVERSITY

THE second article of the constitution of this society begins with the sentence, "The objects of this society shall be the cultivation of clinical research by the methods of the natural sciences; the unification of science and the practice of medicine; the encouragement of scientific investigation by the practitioner, and the diffusion of a scientific spirit among its members."

One need not stop to ask, perhaps, to what extent these objects have been advanced in a material sense since the inception of this society twenty-three years ago. The expansion of the clinics during this period particularly with respect to the provision of more adequate hospital wards, laboratories and equipment for clinical investigation has been phenomenal and is familiar to you all. The funds for carrying on clinical research in these laboratories, though undoubtedly not keeping pace with those that have been provided for bricks and mortar, have nevertheless increased surprisingly and perhaps as fast as is wholesome in a period of rapid expansion, when the finding of men suited for research, by reason of a primary interest in the search for new knowledge and the simultaneous possession of those rare, but essential qualities of initiative and originality, is usually more difficult than the finding of material resources. In spite of this difficulty, the number of those engaged in clinical research has likewise multiplied many times during this period, to such an extent, indeed, that the published products of their labors have resulted in a deluge which at times bids fair to engulf us, whether by volume or by depth, I will leave to you to decide.

While these matters need not detain us, it is, perhaps, pertinent to inquire to what extent the character and direction of clinical research and the nature of the methods it employs have been advanced, or perhaps it would be better to say, have been changed during this period of expansion in material facilities and in human activity; whether in fact these more important aspects of clinical research have kept pace with the evident material progress. To do so, it is obviously necessary to have a clear conception of what clinical research is or purports to be, and also just what is meant by the phrase quoted from the constitution—"by the methods of the natural sciences."

Clinical investigation, if "the unification of science and the practice of medicine" be the worthy goal that the writers of our constitution conceived it to be, should not concern itself primarily with physiology or chemistry, with physics, mathematics, or biology, nor even with the application of these subjects by the physiologist, or chemist, or physicist or biologist to the problems of clinical medicine, but primarily with the study of the phenomena of disease by clinicians thoroughly familiar with disease in all its varied aspects through intimate and constant contact with disease in the field—whether this be in the home, the office, the out-patient clinic, or the wards of the hospital should matter little, provided the contact be comprehensive enough to give a reasonably complete picture of the disease in question.

Furthermore, I believe it should be kept in mind that the purpose of this study of disease should be primarily to find out about disease, largely for the fun of doing it, to discover the circumstances or conditions under which disease develops, the nature and mechanism of the disturbances of function and structure which take place during the course of disease, and the circumstances or conditions under which recovery or death occur. Secondarily, this may lead, and fortunately sometimes will, to the discovery of methods of prevention, amelioration or cure, but these practical and humane purposes should, I believe, be kept in the background, if clinical investigation is not to be too soon diverted and frequently misled in following its main purpose, the elucidation of the phenomena of disease.

In this connection I should like to quote a paragraph by Slesinger[2] in a recent article entitled "The Drift of the Social Sciences."

Social science shares with medical science the necessity of having to free itself of the desire to do good and of

[1] Presidential address, American Society for Clinical Investigation, Atlantic City, May 4, 1931.

[2] *Survey Graphic*, 19: 24, 1931.