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THE INFLUENCE OF CHEMICAL THOUGHT ON BIOLOGY[1]

By Sir FREDERICK GOWLAND HOPKINS

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THE latter half of the last century, though a period of such rapid progress alike in physical and biological science, saw inadequate contact between the thought of the chemist and that of the biologist.

It is true, and a familiar circumstance to those with an interest in the history of science, that, when that half century began, organic chemistry and what we now term biochemistry were both yet in embryo and were hardly to be distinguished. Justus von Liebig fathered them both.

It was the genius of Liebig that started modern organic chemistry on a triumphant career, and Liebig's great desire and one which directed his own efforts was to see chemistry render full service to animal physiology and to agriculture. This desire, in satisfactory measure, was not fulfilled during Liebig's own lifetime, and it is, I think, of some historical interest to decide why during years when scientific minds were so alert so promising a field was cultivated by so few. At first I think certain personal attributes in leaders of thought contributed to the separation of chemistry from biology. Liebig himself, for instance, though so brilliant a chemist, lacked biological training and, as I have always felt, a biologist's instincts. When with great enthusiasm he came to apply his chemical knowledge to the living plant and animal his thought often went obviously astray, and much of his theoretical teaching was instinctively and rightly rejected in biological thought. What was really so valuable in that teaching lost therefore some of its influence. Strange as it may seem, the influence of that other dominant mind of the time, that of

[1] Given at the Harvard Tercentenary Conference of Arts and Sciences, September 8, 1936.

Pasteur, did not altogether favor an approach between chemist and biologist. If Liebig remained too much the chemist, Pasteur, once he entered, with such immense profit to science, the biological field, became almost too much a biologist, at least in so far as he favored the current belief that the activities of a living organism could be understood only by thinking in terms of that organism as a whole. Any analysis of its totality he held to be of little avail.

Although such influences played a part, as did the prejudice of some leading biologists, the chief factor which delayed an approach to biology from the chemical side was doubtless the extreme vigor of the young science of organic chemistry itself. Extraordinary enthusiasm followed immediately upon the activities of Liebig, and the rapid development of the magical synthetic art of the chemist provided him with substances made not by nature but by himself, with properties especially suitable for the development of clear ideas concerning molecular structure. To gain these was the enthusiastic and highly successful effort of the time. There was therefore for a long while relatively little temptation to approach the plant or animal for new material, an approach which might have reawakened biological interests in the mind of the chemist.

Meanwhile the times were not ripe for a serious approach from the side of biology. Zoology and botany were still essentially observational and descriptive sciences, while chemistry was necessarily experimental, a circumstance which in itself helped in their divorce. In the history of biology it was of course inevitable that the study of form should precede the study of function, and it is not surprising that concern with the molecular events which must underlie all displays of active function should come still later.

Moreover, at the very time when Liebig was engaged in urging the claims of chemistry on biological thought, the long and intelligent study of plant and animal forms in nature at large reached its great triumph in establishing the truths of evolution which so profoundly influenced scientific thought. It is not surprising that this new outlook and the many suggestions it gave for yet closer study of morphological differentiation and adaptation left the general biologist preoccupied with the manifestations of form for many years longer.

On the other hand, vertebrate physiology, starting as the handmaid of medicine, was from the first and long remained the most experimental of biological sciences; necessarily experimental because it is concerned with the study of function. Before the end of the last century it had, as you know, accumulated an impressive body of enlightened knowledge concerning the visible functioning of organs. It was in the service of classical physiology that modern biochemistry had its more immediate origin. In its studies of metabolism physiology necessarily entered the chemical field, and though for a long time such studies were somewhat superficial, largely because adequate chemical knowledge was lacking, they prepared the way for the more ambitious efforts of biochemistry to-day.

It is true that in Germany the chemical side of physiology was studied for its own sake and in continuity right from the days of Liebig onwards. This was the case in the University of German Strassburg. Here alone for many years was the subject of physiological chemistry recognized as entitled to recognition as a self-standing scientific discipline, and especially under the influence of the genius and the highly trained mind of Felix Hoppe-Seyler much fine work was done at that center, even during the years of which I have been speaking. At other centers in Germany great physiologists were also concerned with the chemical side of their subject; but there was only rarely any contact between the chemist proper and the physiologist. Until the end of the century the progress of biochemistry remained relatively slow and for the most part consisted in a gradual increase in knowledge concerning the general nature and distribution of the many chemical substances which are to be found in animal and plant tissues. There was also continued enterprise in studies of the metabolic balance sheet of the human body which incidentally led to much, but rather detached, knowledge concerning the end products of metabolism. Little, however, became known of the actual chemical events which occur in the tissues during life.

Apart from the divorce between chemical and biological thought, there was a tendency in the latter which in itself discouraged attempts to probe the secrets of living cells by chemical methods. Most biologists were content to ascribe the internal events of metabolism to the elusive properties of an entity insusceptible of profitable analysis; to the influence of protoplasm as a whole. There was, as I well remember, a wide-spread feeling that chemical studies which interfere with the full integrity of protoplasm could at most have chemical interest and must remain without bearing on the realities of biology. Looking back I find it interesting to recall that it was just when the last century was giving way to this that certain advances occurring together within the space of a year or two greatly helped to change a point of view which for the chemist had been wholly inhibitory. I would instance the publication of Emil Fischer's brilliant work on the chemistry of proteins, the discovery of hormones, and in particular the recognition, too long delayed, of the fact that the progress of chemical events in the living cell is controlled by definite objective agencies, the enzymic catalysts. These and other aspects of new knowledge, revealed together at a critical moment, started biochemistry in its more modern guise on a period of rapid progress which to-day is even accelerating.

Lest they should be unfamiliar to some, I will venture to put before you in fewest possible words an appraisement of the present position and outlook of this branch of science and will endeavor to convince you that its facts are significant.

From the first, modern biochemical inquiry has had ambitions beyond that of determining the nature of the materials with which the processes of life make play, essential as such knowledge is for its progress. Its claim to be an independent branch of inquiry is and must be based on success in describing the molecular events which underlie the manifestations of life wherever they occur. It is dealing, and must deal to the best of its ability, with the living and not with the dead. Success in such endeavor is recent but is not to be thought of as altogether new. During many years a few individual workers dealing chiefly with evidence yielded by the intact organism doubtless brought to light facts bearing significantly upon the nature of chemical events as they occur within the living tissues. But such workers have till recently been rare, and the facts won were too isolated to form a significant body of knowledge. The last twenty-five years, however, have seen, together with important advances in technique, an extraordinary growth of interest in the chemical dynamics of living tissues. Recruits to their study have become very numerous, and publications concerning them appear in large numbers. There is now much knowledge of a consistent and coherent kind, as well as a large harvest of facts ready to fall into place as knowledge further advances.

You will not expect in a brief address any discussion of technicalities either of methods or results. I will deal with certain aspects of the newer knowledge on the broadest lines possible. How many and how diverse are the chemical reactions which support even some of the apparently simplest displays of function—the contraction of a muscle, for instance—is becoming daily more evident. Many of these individual reactions are being isolated from living systems and maintained in progress for successful study *in vitro.* They are found to progress because controlled by specific catalysts—the intracellular enzymes—and knowledge concerning the nature of these activating agencies, though far from complete, is rapidly growing. In not a few instances it has proved possible to follow *in vitro* reactions still proceeding in that ordered sequence which (as we have now a right to assume) reproduces their essential relations in life. In particular has success been met in the study of reductions and oxidations in living cells; all important among biochemical reactions as providing energy at the right time and in the right place for the physiological functioning of each cell or organ.

Important to productive thought about such matters is the growing assurance that the structure and configuration of molecules, which organic chemistry determines to-day with increasing accuracy and in great detail, have as great a share in deciding the origin, the influence and the fate of substances in living systems as it has in the laboratory. This was formerly disbelieved or ignored by those who were content to ascribe all chemical events in a living cell to the influence of protoplasm as an entity; real in its activities only when intact. The biochemical outlook could not fail to be widened and chemical thought concerning living organisms stimulated when physiological studies first revealed the existence of hormones and the general nature of their functions. In this field, in the specific activities of hormone, and of vitamins—which can be justifiably spoken of as exogenous hormones—we have outstanding examples of the dominant influence of molecular structure, which in the case of many of these agencies is already known. We find among them diversity of structure associated with diversity of action, and are learning that, just as in the laboratory, so in living systems, there is first the influence of molecular type and then the added influence of special atomic groupings. Also as in the laboratory certain modifications in the molecule may have relatively little influence upon its physiological activity; others may profoundly modify it. It is well to recognize how dominant is this influence of molecular pattern—the special concern of the chemist—throughout the realm of life.

Biochemical studies, owing to their early origin from the medical field, have long dealt chiefly with the mammal. If, however, the science is to arrive at significant generalizations, to decide, for example, what, in a chemical sense, is essential to the fundamental manifestations of life, and what is only essential for some specialized function, it must extend its studies into fields as wide as possible. Fortunately, associated with growing activities in the field of general physiology, there is to-day an increasing interest in comparative biochemistry, and much of fundamental importance is being learned from its pursuit. Comparative studies have led to an acute realization of the fact that biochemistry can render important help towards an understanding of development, of evolution and of heredity. Chemical differentiation underlies, or is associated with morphological and functional differentiation, and to learn exactly what is the nature of such association is a fascinating task ahead. Of great promise for future studies is the recent proof, first that definite chemical substances are concerned in evoking specifically important stages in the morphological differentiation of the growing embryo; and, second, the indication that recognizable chemical factors, present in the genetic constitution of germ or sperm, are concerned in the carriage of the hereditary characters which appear in the developed organism. Further, we find in passing from one group of organisms to another that a given chemical function may be served by different though related substances. There is a chemistry of species. To all such conclusions the study of the plant is contributing no less than that of the animal. Much aid to biochemical thought, moreover, is coming from the studies of micro-organisms; studies which deal with them not from the standpoint of pathology, but from that of general biology; recognizing them as living systems with chemical activities and potentialities which partake of the marvelous. The field of biochemical investigations has now indeed become very wide. It would seem that chemical thought must accompany biological thought wherever it is employed.

So rapid a review as that I have put before you provides but a poor measure of the amount of progress made, but for those who were not previously familiar with the aims and activities of a relatively new branch of science it will perhaps suffice as an indication at least of their nature.

I would like to remark here that, partly perhaps because of the special interest involved in the constitution of substances so remarkable in their functions as hormones and vitamins, many eminent organic chemists with their special intellectual equipment have of late been attracted into the biological field, and other aspects of biochemistry are receiving increasing attention from highly qualified physical chemists. No branch of science will benefit more than biochemistry from those newer methods of study and newer conceptions which chemistry is just now receiving from physics. All this is of happy augury. So many problems await the united efforts of the physiologist and the pure chemist with the specialized biochemist acting as a necessary intermediary.

To the branch of science of which the aims and claims have been before you the contributions of American workers have been exceptionally great. All those, like myself, to whom it has been the concern of a lifetime owe a deep debt to this country.

At a time when, save in Germany alone, the subject was receiving scant attention in Europe, where academic recognition of its needs was almost absent and workers very few, many able investigators were already engaged upon its problems here. Posts, moreover, were provided for them at not a few centers carrying titles which implied that the subject was worthy of regard as an independent scientific discipline, a recognition then rare elsewhere. The lead given to it in America is clear to those directly concerned with biochemistry, and it is made patent to all readers of Dr. Russell H. Chittenden's admirable book, "The Development of Physiological Chemistry in the United States." In that book it is also made clear how, and by whom, the seeds were sown from which grew that early wide and generous interest in the subject. They were sown by Dr. Chittenden himself. So far back as 1874 he was placed in charge of the first definitive laboratory of physiological chemistry in America which had its place in the Sheffield Scientific School at Yale University. This was but a small beginning, and at that time Germany alone could provide the knowledge and experience necessary for the teacher and investigator. The year 1878 therefore found Chittenden at Heidelberg working under Willy Kühne, in whose laboratory the knowledge and experience then available were present in full measure. It is interesting to learn from Dr. Chittenden that his choice of Heidelberg was intuitive. It was an intuition which fully justified itself. With the experience gained, and with Kühne's inspiration added to his own innate gifts, Chittenden returned to a chair of physiological chemistry at Yale, a post which he occupied for forty productive years.

Much good work was done during the last two decades of the nineteenth century, but, as Chittenden himself points out, the study of the subject was limited in outlook till near the end of that period, because it was taught almost exclusively from the standpoint of medical needs. Medicine has been the foster parent of the biological sciences and can thus claim their loyalty, but medicine has sometimes kept them too long in leading strings; not always realizing their capacity for independent growth. It was mainly with dead materials and the composition of secretions and excretions that physiological chemistry was mainly concerned, subserving the then limited demands of medicine. Only a few—in America, for instance, Newell Martin and Chittenden—foresaw that its potentialities were much greater and urged that it should widen its activities. I have earlier claimed that it was just at the turn of the century that biochemistry entered upon a new period of growth and undertook its more dynamic studies. This is well illustrated by the circumstance that in America a number of brilliant investigators rather suddenly entered the field in the opening years of the present century.

I would very much like to pay a tribute to some of these. So many are worthy of mention, however, that it is difficult to avoid the invidious task of selection. Perhaps you may let me mention a few to whom I myself was especially indebted in those days, confining my references rather strictly to those whose work was in progress before the end of the first decade of the century. These were pioneers in the newer phase of biochemical progress. I will begin by mention of

Christian A. Herter, whose work began and, alas, also ended during the period with which I am dealing. Directly and indirectly Herter served biochemistry well; directly by his own work, indirectly in many ways, but especially in two. The *Journal of Biological Chemistry,* which he founded and financed, has for more than thirty years continued to publish the results of researches, very many of which are among the most important ever carried out in the subject. But Herter also fostered the genius of Henry Drysdale Dakin, and for that our debt to him is great. Dakin during the period of which I speak brought to the field of biochemistry great technical skill inspired by real chemical vision, together with an instinctive grasp of the nature of biological problems. He has never ceased to serve the subject nobly. I will next mention one who was a senior among these pioneers. His classical work upon the endocrine secretions began before the century, but it continued during those first ten years. He has done much admirable work since and has guided the thought and work of many younger men into profitable channels. To John J. Abel biochemistry owes much. The work of Otto Folin at Harvard stands out especially because of the help it gave, then and afterwards, to the efforts of others. In the fertile production of new methods of analysis Folin was supreme. Apart from this, however, our knowledge of metabolism would have had serious gaps had his own fine work been lacking. Lawrence J. Henderson's thought and work were in full activity during the period of which I am thinking, and just at its close appeared a classical publication on the equilibrium between bases and acids in the animal body which led the thought of every biochemist along new and productive lines. What he did then, and all that he has done and taught since, called for that rare and philosophical quality of mind which he possesses in full measure. Thomas Burr Osborne's invaluable work on the chemistry of proteins which began before, but continued through these years, can never be forgotten. His extraordinarily profitable partnership with Lafayette B. Mendel to which we owe so much of our knowledge concerning the biological value of proteins began just after the decade closed, but I may be allowed to pay a tribute of admiration to the enterprise. The work of Henry L. Wheeler and Treat B. Johnson at Yale, and the later work of the latter alone on the pyrimidine bases, involved constitutional studies of the highest value to biochemistry, and equally valuable was that of Walter Jones, at the Johns Hopkins University, on nucleic acid and related subjects. The work of Phoebus Levene during those early years was also devoted to nucleic acids and was most valuable. The brilliant and innumerable constitutional studies he has carried out in later years represent great accomplishment. From the Hull Physiological Laboratories A. P. Mathews was publishing his earlier researches dealing with physicochemical problems of much interest.

Apart from the work of those recognized officially as biochemists the subject in those days was benefiting greatly if indirectly, from the all-important calorimetric studies of Francis Benedict and Graham Lusk. To personal friendship with the latter and to the stimulating influence of his thought I myself owe more than I can tell. From his great book on nutrition I have derived many a lecture to students; I fear without due acknowledgment.

In the years which have followed on this pioneer period biochemistry in America has received increasing recognition, and in the hands of very many highly qualified investigators, working at numerous centers, has achieved remarkable successes. Among the many who have helped this recognition and contributed to the high accomplishment the nature of this occasion allows me the pleasure of mentioning just one. I have remarked already that, recently, the professed biochemist has fortunately gained the interest and the help of eminent organic and physical chemists which, except for the great services of Emil Fischer, it for a long time lacked. Among these is one who is equally eminent in both these branches of chemistry; I mean the distinguished president of Harvard University. Dr. Conant's work on chlorophyll and on blood pigments is of outstanding importance, and no less important are his enlightened studies of reduction and oxidation potentials which bear with the utmost significance on urgent biological problems. No one who takes pleasure in the growth of the subject can fail in gratitude to the president.

The activities which have been and are so notable in this country are now extending to every land where science is cultivated at all, and the attention given to biochemical problems is everywhere still increasing. Seldom, I think, in the history of science has any branch of inquiry enjoyed so great an impetus.

What, you may ask, from the standpoint of pure knowledge is the goal of these intellectual activities and what will be their ultimate accomplishment? I have faith that in the end they will reach to a description of living systems which, in so far as they are chemical systems, may be complete. From a knowledge of individual events they will proceed to an understanding of the organization of these events; that organization which makes the organism. I can see no obstacle to the attainment of such an intellectual synthesis of knowledge. When that synthesis comes it will involve a full understanding of many of life's visible manifestations, which is of course not to say that it will define life itself.

If, however, the claim of biochemistry is to describe life, at any level, in chemical terms it may come more under the eye of philosophy than perhaps any other branch of biology. There are schools of philosophy which will continue to ignore facts of a kind accessible to the chemist as being without significance in their search for reality; but there are other schools which will at least take note of them. In any case there are biologists with philosophical leanings who still suspect that biochemical facts are of chemical interest only.

The chemist on the other hand hopes to gain real understanding from his own standpoint of whole organisms through his study of their parts.

But these are days in which there is much insistence on the view that in the world-scheme only wholes can partake of reality. The truth that the whole is something different from the arithmetical sum of its parts, felt vaguely, but almost instinctively, even by commonplace and uninstructed minds, has been sublimated and raised to the status of a philosophical doctrine.

It is impossible at Harvard to forget the teaching of that profound philosopher, Alfred Worth Whitehead, who came one day to Cambridge from Cambridge. We have his assurance that the conception of organism must replace in thought the abstract entities which were the units of Newtonian physics. Reality always involves relations, internal and external; while an event, and not any static entity is the unit of things real.

Biology from its very nature has never been much tempted to abstraction, and for it the organism has always been the only significant unit; while the living organism as it exists in time is essentially a directed event. The question that arises is whether the modern biochemist, in analyzing the organism into the parts which he is best able to study, has so departed from reality that his studies have no longer biological meaning. I myself would venture to answer that question by saying that so long as his analysis involves the isolation of events, and not merely of substances, he is not in danger of such departure. We should learn little about the nature of an organism by being shown a collection of every substance it contains in stoppered bottles, however well known the constitution of each. Each isolated event on the other hand partakes, at least, of the nature of the whole organism. Even if on occasion it is but a single specifically catalyzed biochemical reaction it remains an event controlled and directed. True it has lost the influence of the environment which is provided by the whole organism, and its progress may thus be modified in detail, but in detail only, not in its essential nature.

I do not find that Professor Whitehead doubts the validity of such an approach to the biological whole through its chemical parts. In his Lowell Lectures published in the book, "Science and the Modern World," while claiming that, because of its concern with organism, the physiological standpoint "put mind back into nature" he remarked that "viewing the question (of organism) as a matter of chemistry, there is no need to construe the actions of each molecule in a living body by its exclusive particular reference to the pattern of the complete living organism." He suggested that each molecule may be so affected by the pattern of the whole living system as to be otherwise than what it would have been if placed elsewhere; but remarked that "it would be entirely in consonance with the empirically observed action of environments if the direct effect of aspects as between the whole body and its parts were negligible." It is true, of course, that no molecule when actually playing a part in dynamic events within an organism remains the same as when it contributes to the contents of a bottle on the shelf of the chemist. It is different because it is activated, and may be undergoing transition. The precise state at a given moment of every molecule in a living cell is doubtless determined by the state of the whole cell at that moment. Such relations, however, though so complex, are not of a kind which need escape the ultimate power of experiment to define.

It is sure, I think, that biochemical facts and biochemical thought will provide fresh aspects for biological thought. They will no less strengthen the ability of biological science to serve humanity.

It is sure that if he can add to what the eye itself reveals an adequate mental picture of the invisible molecular events which underlie the visible, the biologist will gain increased understanding of the behavior of every living thing. The physiologist too will add to his understanding of every organic function; and the clinician, no less than the pathologist, will acquire a deeper insight into the significance of every departure from the normal. This is my faith, and I hope it may be yours.

SCIENTIFIC EVENTS

VISCOUNT GREY MEMORIAL

THE following appeal, setting forth the form of the memorial by which it is proposed to commemorate the late Viscount Grey of Fallodon, has been issued:

More than two years have gone by since the death of Lord Grey of Fallodon. The time has come when the affection and admiration which he inspired among so many of his countrymen should find expression in some permanent memorial.

He is remembered as the statesman who fought so long and so hard the losing battle for European peace; and