Otto Meyerhof: 1884–1951

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WITH THE DEATH of Otto Meyerhof on October 6, 1951, the world lost one of the most outstanding scientists of this century. The revolutionary character of his thinking, the originality of his approach, and the brilliance of his experimental work had a profound influence upon the progress of physiology and biochemistry—indeed, upon the progress of biology as a whole, and consequently upon the medical research of the past few decades.

The significance of Meyerhof's scientific work cannot be appreciated without an understanding of the breadth and richness of his rather unique personality. To many biologists it may be surprising not only that Meyerhof graduated, in 1909, at the University of Heidelberg as a doctor of medicine, but that his thesis dealt with a problem in psychiatry. In fact, at that time he was mainly interested in psychology and philosophy. During this period Meyerhof was closely associated with a group led by Leonard Nelson in Göttingen, whose teaching largely followed Kant and Fries, although with some modifications. He had first come in contact with Nelson during his high school days. His serious concern with philosophy is further indicated by the fact that he was for many years editor of the *Abhandlungen der Friesschen Schule,* where Nelson and his group published.

Following his graduation he entered the medical clinic of Ludwig Krehl, an outstanding pioneer in promoting the introduction of physiological thoughts and methods in the approach to medicine. Krehl's book *Pathologische Physiologie* is considered by many to be a landmark in modern medicine. In Krehl's clinic Otto Meyerhof and Otto Warburg, who were to be the most prominent biochemists of our time, first met. This meeting, which had considerable influence on the subsequent development of these two men and of biochemistry, was essential in stimulating Meyerhof's interest in what was to be his lifework. In the following years Meyerhof and Warburg worked repeatedly at the Marine Zoological Laboratory in Naples and collaborated in studies on the metabolism of sea-urchin eggs. In those days the Naples laboratory was a meeting place for biologists from all parts of the world, as the Marine Biological Laboratory at Woods Hole is today.

An illuminating insight into Meyerhof's early approach to the study of life processes is given by his article "Zur Energetik der Zellvorgänge," delivered in 1913 as a lecture at the University of Kiel, which he had just joined as a *Privatdocent.* This paper clearly shows that his approach was essentially intellectual and philosophical. It reveals also the extraordinary depth of his knowledge and his remarkable ability to integrate a variety of physical, chemical, and biological phenomena.

At the turn of the century there was considerable interest in the question of whether the heat evolved by the animal body could be accounted for by the energy liberated through combustion of foodstuffs. Meyerhof was not satisfied with a merely affirmative answer to this question; he wanted to know how the potential energy of foodstuffs is made available to the cell. He recognized that between the initial energy input, in the form of foodstuffs, and its final dissipation as heat a series of energy transformations may occur. These transformations may serve to maintain the living organisms in the living state, which he clearly recognized as a dynamic equilibrium. It is easy to imagine that these ideas, which became the basis of his lifework, would produce a profound impression in the whole scientific world. Jacques Loeb invited him to write a somewhat enlarged version of the abovementioned paper for his "Monographs on Experimental Biology." It appeared in this country in 1924 under the title "The Chemical Dynamics of Life Processes." The ideas expressed in this essay are so much alive today that it is still highly recommended to biology students at Harvard as an introduction to the physicochemical approach to the study of life processes.

When Meyerhof approached the problem of the conversions of chemical energy in the living cell, he chose muscle as the experimental material. This choice was prompted by the recognition that muscle offered an excellent opportunity to correlate chemical transformations with the production of both heat and mechanical work.

When he started these investigations, the formation of lactic acid, demonstrated by Fletcher and Hopkins in 1906, was about all that was known of the chemical reactions associated with muscular contraction. The source of this compound, the way in which its formation provides energy, and the manner in which the energy is utilized were completely obscure. A. V. Hill's measurements of heat production by isolated frog muscle during activity and subsequent recovery had demonstrated, not only that the heat evolved was proportional to the work performed, but also that about half the total heat was actually evolved during recovery. Meyerhof demonstrated that muscle glycogen is the precursor of the lactic acid formed in the absence of oxygen. He further showed that, in the presence of oxygen, some of the lactic acid formed during the anaerobic contraction was oxidized, but that not all the lactic acid underwent this fate. About one fifth to one fourth of it was oxidized to carbon dioxide and water, and the energy of this oxidation was used to reconvert the remaining four fifths or three fourths to glycogen. His discovery thus confirmed and extended Pasteur's hypothesis that fermentation (or glycolysis) is *"la vie sans air"* in that, to a certain extent, it substitutes for respiration. His observations actually proved Pasteur's assumption that less carbohydrate is consumed in the presence of oxygen than in its absence. The depression of glycolysis by respiration has since been referred to as the Pasteur-Meyerhof effect. Meyerhof's brilliant analysis of the glycogen-lactic acid cycle and its relation to respiration explained the course of the heat production and, for the first time, established the cyclic character of energy transformations in the living cell. For this accomplishment Meyerhof received the Nobel prize in physiology and medicine in 1923 (when he was only 39 years old), together with his colleague and friend A. V. Hill.

If we look back on this period today, we realize that it was just a beginning for Meyerhof. In 1925 he succeeded in extracting the glycolytic enzyme system (the system of catalysts responsible for the conversion of glycogen to lactic acid) from muscle, as Buchner and Harden and Young had previously done with yeast. This accomplishment proved to be the turning point in the elucidation of the entire process of glycolysis. He had already recognized the biological importance of the work of Harden and his associates and of Neuberg on yeast fermentation. In a series of studies in 1917 and 1918 he discovered the ubiquitous presence of Harden's fermentation coenzyme (cozymase) in animal cells, and in a classical paper entitled "Ueber das Gärungscoferment im Tierkörper" he described this finding and discussed the significance of the coenzyme in cell metabolism. Here the beginnings of his ever-increasing conviction of the fundamental unity and similarity of metabolic processes throughout the living world can already be seen.

The clarification of the nature of energy transformations in muscle and of the basic mechanisms of glycolysis was enormously stimulated by the discovery of two phosphorylated compounds in muscle: phosphocreatine (Fiske and SubbaRow, 1926; P. Eggleton and G. P. Eggleton, 1926) and adenosine triphosphate, now widely known as ATP, isolated simultaneously a few years later by Lohmann in Meyerhof's laboratory and by Fiske and SubbaRow. One of Meyerhof's most important contributions was the discovery of the high-energy content of these compounds, which he found by measuring the heat produced when they are hydrolyzed with liberation of inorganic phosphate. This discovery revolutionized current concepts of muscular contraction and cellular metabolism.

The enzymatic breakdown of phosphocreatine and ATP in muscle was soon recognized to yield energy for muscular contraction more directly than does the production of lactic acid. For this development a discovery by Lundsgaard was essential. Lundsgaard found that muscles poisoned with iodoacetic acid can contract, without producing lactic acid, at the expense of phosphocreatine breakdown. Further observations in Meyerhof's laboratory, both on muscle extracts and on the intact muscle, demonstrated that the breakdown of ATP precedes that of phosphocreatine and is the process that serves as the primary source of the energy for muscular contraction. The sequence of the various chemical events in contracting muscle was analyzed by Meyerhof and his associate in a most elegant way by employing sensitive physical methods (transmission of light, volume, and pH changes) that could be correlated with the different chemical reactions. These studies culminated in the conclusion that both lactic acid production and phosphocreatine breakdown participate indirectly in muscular contraction by making possible the resynthesis of the ATP utilized during muscular activity. These investigations are a classical example of the successful use of physical and chemical methods in the analysis of cellular function.

Meyerhof's conviction that the same fundamental mechanisms are used repeatedly in nature persistently led him to study the occurrence of important reaction patterns in various phyla. His interest in comparative biochemistry led to the discovery of phosphoarginine in the muscle of invertebrates, where it replaces phosphocreatine and performs the same function.

Although phosphocreatine and phosphoarginine were found to participate exclusively in the metabolism of muscle, ATP is now known to participate widely in reactions involving energy transfer in all cells: its energy can be converted to mechanical, osmotic, and electrical work, as well as into light energy, and can be used to promote a number of synthetic reactions not only in carbohydrate metabolism but in nearly all biosynthetic processes. The discovery of ATP thus was the key that opened the gates to the understanding of the conversion mechanisms of metabolic energy. The reconstruction *in vitro* of the complicated chain of reactions of glycolysis and alcoholic fermentation, in which ATP plays an essential role, is one of the most outstanding achievements of modern biochemistry. Meyerhof's name is inseparably associated with this development, along with the names of Harden, Young, Robison, Neuberg, Parnas, Embden, Warburg, D. M. Needham, and the Coris, among others.

In discussing the mechanism of resynthesis of ATP through the oxidation-reduction reaction of glycolysis, Meyerhof created the expression "energetic coupling" between oxidation and phosphorylation. The mechanism of the coupling was eventually elucidated through the work of Warburg, who demonstrated the generation of carboxyl-phosphate in the process of oxido-reduction.

Today this step-by-step development of the intermediary reactions of the glycolytic cycle stands out as one of the greatest of Meyerhof's accomplishments. Starting with the analysis of the chemical changes associated with muscular contraction, and going deeper and deeper into the analysis of the basic mechanisms involved, he eventually obtained the answer to the question he had raised in his youth when he lectured on the dynamics of life processes. He showed that metabolic energy passes through a series of transformations that make it available for the energy-requiring processes of the cell. Many types of cells can obtain the necessary energy exclusively through glycolysis or fermentation, whereas other cells can, in addition, use respiration as a more efficient source of metabolic energy. As is now known, the utilization of metabolic energy through respiration or through glycolysis occurs in essentially similar ways. Thus the analysis of the glycolytic cycle was the clue to the understanding of the fundamental mechanisms of energy generation in all living cells.

In the midst of his most active and creative period, political events forced Meyerhof to leave Germany in 1938. During the preceding 20 years his laboratory facilities had constantly improved. In Kiel, where he had been Professor Extraordinarius since 1918, he established a warm and close relationship with Rudolf Höber, one of the most prominent general physiologists in Germany. This association was certainly fruitful for Meyerhof's scientific development. His facilities at Kiel were rather limited, however. In 1924 he moved to the Kaiser-Wilhelm Institut für Biologie in Berlin-Dahlem, where he became head of a division.

Dahlem was at that time one of the greatest scientific centers in the world. A group of extraordinary men was gathered there in the various Kaiser-Wilhelm Institutes. Meyerhof found his old friend Otto Warburg in the Biology Institute. Carl Neuberg was at the Institute of Biochemistry. Among other names of world renown may be mentioned Fritz Haber and his associates Ladenburg, Polanyi, and Freundlich, at the Institute of Physical Chemistry; and Otto Hahn at the Institute of Chemistry. In many of the seminars held at Haber's institute one could frequently find several Nobel prize winners joining in discussion. Dahlem's stimulating atmosphere and the close contact with these outstanding personalities had a profound influence on Otto Meyerhof.

The facilities that Meyerhof had at Dahlem were not yet adequate for the wide scope of his interests. Therefore, in 1929, when he had the opportunity to join a new institute that he himself could design and plan with all the necessary facilities, he accepted an offer to go to Heidelberg. The Heidelberg Institute was one of the finest of its kind and was ideally suited for his varied research activities. Here he again came in contact with his old teacher Krehl, who was director of the Department of Medicine, as well as the administrative head of the institute.

It is not difficult to realize how hard it must have been for Meyerhof to leave his wonderful institute and his staff of excellent and devoted collaborators. He went first to Paris, where he was warmly welcomed and well received. Through the combined efforts of the late Jean Perrin, René Wurmser, and Henri Laugier, he was appointed director of research at the Institut de Biologie Physico-Chimique. With his untiring energy he immediately started to build up his laboratory under rather difficult conditions. Nevertheless, his productivity continued, as several important papers on the oxidation-reduction phase of glycolysis and the properties of the triose phosphates, as well as the demonstration that phosphorylation is necessary for the biological breakdown of carbohydrate in all cells, bear witness. As he expressed it later in a review article, nonphosphorylating glycolysis is nonexistent except in the imagination of a few people.

When the Nazis invaded France, he and his wife, Hedwig, had to flee under most difficult and trying circumstances. They took refuge in the south of France and eventually, with the help of American friends, the Rockefeller Foundation, and the active interest and efforts of A. N. Richards and D. W. Wilson, they managed to reach the United States at the end of 1940. Meyerhof was appointed research professor of physiological chemistry at the School of Medicine of the University of Pennsylvania, a position he held until his death.

Hardship and suffering, of which the Meyerhofs had no small share, failed to undermine his spirit. The laboratory at Philadelphia was not a large one, but he continued to work actively and productively, as shown by the number and importance of his publications during the past few years. More than 50 papers appeared during this period, bringing the total of his publications to about 400. This amazing productivity is all the more remarkable if one considers that his health was undermined by a severe heart attack suffered in 1944 at Woods Hole, where he spent most of his summers following his arrival in this country. Through the devoted care of his wife he was able to surmount his difficulties and to continue his activities with undiminished energy, until a second heart attack led to his death, which came suddenly and without suffering in the midst of creative work and the preparation of various projects for the future.

During the past few years Meyerhof had discovered the mechanism by which hexose disphosphate accumulates during the fermentation of glucose by yeast extracts (Harden-Young reaction). He demonstrated that this was due to the absence of the enzyme adenosine triphosphatase (ATP-ase), which dephosphorylates ATP. On addition of ATP-ase the yeast extracts fermented glucose to alcohol and carbon dioxide in the same way as living cells. Incidentally, he also succeeded in partially separating muscle ATP-ase from myosin and obtained the enzyme in soluble form. Concentrating his interest on observations made by Axelrod and his collaborators, he demonstrated that a transphosphorylation from substances such as glucose-1-phosphate, phosphocreatine, or acetyl phosphate, to acceptors such as glycerol or sugars, is catalyzed by phosphatases in the absence of ATP. Such transphosphorylation seem to go preferably from higher to lower energy phosphates. His measurements of the equilibrium constants of the hydrolysis and synthesis of phosphate esters and of the conversion of phosphopyruvate and ADP to pyruvate and ATP permitted an accurate calculation of the energy contained in some of these compounds. Quite recently, still intensely interested in the energy content of key metabolic intermediates—so important for an understanding of the mechanisms underlying the biological utilization of metabolic energy—he measured the heat produced on hydrolysis of various compounds, thus rechecking on some of his old measurements and adding new important data to our knowledge in this field.

The impact of Meyerhof's personality and of his work is perhaps best illustrated by the great number of scientists who received inspiration and training in his laboratory. His pupils came from all parts of the world; many of them have not only developed his ideas further, but have opened up new fields of investigation and created, in their turn, schools which have been referred to as the "second Meyerhof generation." An impressive demonstration of his influence was the tribute paid to him by his pupils and friends on his sixty-fifth birthday. He was given a book entitled *Metabolism and Function,* comprising papers by many of this generation's most brilliant scientists in physiology and biochemistry. This was an expression not only of admiration and respect, but also of the ties of affection by which his pupils and colleagues felt bound to one in whom they saw an understanding and devoted friend. Many honors were bestowed upon him by his colleagues and by scientific societies, such as the National Academy of Sciences (U. S.), the Royal Society of London, the Harvey Society, and many others.

At a symposium on phosphorus metabolism held at Johns Hopkins University in June 1951, which, as Bentley Glass pointed out, dealt with virtually every aspect of the chemistry of life, Meyerhof made a masterly introduction, which he closed with the following words: "Just as the role of iron in biological reactions is now made completely understandable by the work of Otto Warburg as being necessary for the catalysis of oxygen transfer, so the role of phosphate compounds in the organisms is made understandable by their importance for energy transfer." It may be added that the work of Otto Meyerhof made this understanding possible.

Meyerhof was one of the greatest thinkers among the biologists of our time. He repeatedly raised the question of the philosophical basis and background of physiology and the relation of life phenomena to physics and chemistry. He staunchly supported the view that the laws of physics and chemistry must be applicable to the forces acting in the living organism. He was convinced that many of the manifestations of life will eventually become understandable in physicochemical terms, and he fought vigorously against vitalistic and neovitalistic views. It is in this light that one must consider Meyerhof's views on Goethe's scientific writings, especially his theory of colors. In a critical essay presented at the Goethe bicentennial celebration of the Rudolf Virchow Society in New York a few years ago, Meyerhof accepted Goethe's contributions in the descriptive field; but when Goethe contradicted the views of Newton, he came in conflict with the laws of physics because his method of approach was not adequate. As Meyerhof emphasized, however, the scientific analysis of nature was not Goethe's real goal. It was the search for the deeper meaning of creation—*"die Ahnung des Ewigen im Endlichen,"* to use the words of Fries. In Meyerhof's basic philosophical attitude, physics and chemistry are only *one* aspect of the world in which we live. Deeply influenced by the transcendental idealism of Kant and Fries, he was constantly aware of other aspects belonging to a category that cannot be analyzed by physicochemical methods. He felt that, in the last analysis, the whole of scientific truth becomes relative to other values which refer no longer to things that may be recognized by our senses, but to what is beyond those things—the meaning of the world.

Meyerhof had a genuine enthusiasm for art, poetry, and literature and a deep interest in archaeology and history. His knowledge in these fields surprised even highly specialized experts. Very few people know that he liked to write poetry. His poems, which are of great intellectual depth and exquisite beauty, reflect a keenly sensitive spirit. His philosophical background, the tremendous range of his knowledge, the remarkable gift of integrating a great variety of phenomena, the originality of his ideas, and the elegance of his methods—all these factors contributed to making his work outstanding and may account for the extraordinarily wide scope of his achievements. The combination of a great scientist and a great man made him a real leader and one of the most distinguished representatives of modern science.