

# Cells Flexing Their Muscles

When a heart beats or the body is fighting a cold, one molecule that supplies the energy for these processes is always involved: adenosine triphosphate. Its central importance for metabolism was discovered about 80 years ago by biochemists **Karl Lohmann** and **Otto Fritz Meyerhof** at the **Kaiser Wilhelm Institute for Medical Research** in Heidelberg.

TEXT **MAREN EMMERICH**

Berlin, December 1928: In the Physiology Department of the Kaiser Wilhelm Institute for Biology, Karl Lohmann seems spellbound by the hydrochloric acid bubbling in the flask in front of him. It contains a very special substance that Lohmann has just isolated from fresh rabbit muscles, and that has been simmering in the acid at 100 degrees Celsius for seven minutes.

Now the chemist adds molybdenum solution – and the contents of the flask turn blue. This means that the substance obtained from the muscle has released phosphate. Lohmann also identifies adenine and pentose phosphoric acid as additional daughter products, and succeeds in determining the proportions of the individual components. He calls his product “adenylpyrophosphoric acid,” and publishes his discovery in the journal *NATURWISSENSCHAFTEN* on August 2, 1929, under the prosaic title “On the pyrophosphate fraction in muscle.”

This article is probably one of the most-cited works in the whole of biology today, marking as it does the discovery of the universal energy source of the living cell – adenosine triphosphate, or ATP for short. ATP consists of one molecule of the base adenine and one molecule of the sugar ribose, with three phosphate groups attached.

In the summer of 1929, Karl Lohmann presented ATP at the International Physiological Congress in Boston, but neither his lecture nor the publication aroused much interest among his colleagues. Further tests were needed to discover the role of adeno-

sine triphosphate in the body, and Lohmann and his superior, physiologist and Nobel laureate Otto Fritz Meyerhof, devoted themselves intensively to this task in the years that followed.

Meyerhof came from a prosperous German Jewish family. Born in Hanover in 1884, he spent most of his childhood and youth in Berlin, where he completed his schooling in 1903 and began to study medicine. Initially, his scientific interests were in psychiatry and philosophy. He obtained his doctorate in 1909 under Franz Nissl in Heidelberg, with a thesis on the “Psychological Theory of Mental Disturbances.”

As an assistant at the Heidelberg Clinic, he worked with Otto Warburg, who would later be known for his discoveries on the development of cancer cells, and became Founding Director of the Kaiser Wilhelm Institute for Cell Physiology in Berlin in 1930. It was under Warburg’s influence that Meyerhof’s interest in muscle metabolism was kindled, and this formed the focus of his research when he moved to the University of Kiel.

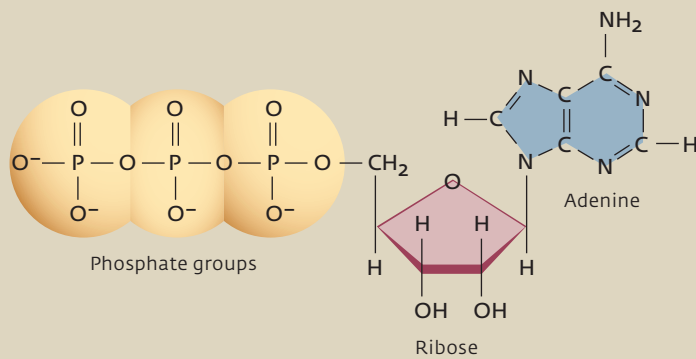
When muscles work in anaerobic conditions – without the presence of oxygen – lactic acid is formed, with its three carbon atoms. As soon as oxygen is added to the mix, the lactic acid disappears again. This reaction always consumes precisely the amount of oxygen needed to oxidize one-fourth to one-sixth of the lactic acid, while the cell converts the rest back into the storage substance glycogen.

Otto Meyerhof detected these fixed quotients between the total lactic acid consumed and the oxidized portion. The discovery won him the Nobel Prize for Medicine in 1922, and the quotient still bears his name. As a result of this distinction, Meyerhof, who was still working as Rudolf Höber’s assistant in Kiel, was offered a professorship in the US. However, he decided instead to accept an offer from the Kaiser Wilhelm Society, and in 1924, took over as head of the Physiology Department at the Kaiser Wilhelm Institute for Biology in Berlin. Soon afterward, he recruited chemist Karl Lohmann, who had just obtained his doctorate.

Lohmann was born in 1898 as the fifth child of a farming family in Bielefeld. In 1919, after the First World War, he went to Münster to study chemistry, moving to Göttingen three years later. It was there that he obtained his doctorate in 1923 with a thesis on montana resin. He had been fascinated by physiological questions

Sir Archibald Hill (seated, right), who shared the Nobel Prize for Medicine with Otto Meyerhof (seated, left) in 1922, visited Meyerhof’s research group in Heidelberg in 1930. Standing behind the Nobel laureates at far left is Karl Lohmann, who discovered ATP.





ATP, the molecule that summarizes the energy of life in three letters, consists of adenine, ribose and three phosphate groups. The elimination of a phosphate group generates energy that the cell can use in many ways.

during his studies, and he devoted himself to these issues after graduating. Before joining Meyerhof's group, he had published two works as a trainee at Göttingen's Pharmacology Institute, on the status of cholesterol in serum and a method for determining cholesterol levels in serum.

Karl Lohmann's practical skills turned out to complement Meyerhof's theoretical talent extremely well, the latter having maintained his interest in philosophy and been joint series editor of *ABHANDLUNGEN DER FRIESSCHEN SCHULE (The Proceedings of the Friesian School)* for a number of years.

The two scientists realized that the elimination of a phosphate residue from the ATP molecule enables muscles to contract. This reaction releases almost exactly the same amount of free energy

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It is surely no exaggeration to position ATP alongside DNA, the molecule that bears our genetic information. One [molecule] holds the key to the energy of life, and the other to its genetics, each in three letters – three letters that signify, aside from complex chemistry, no less than the building blocks of our mechanistic worldview reduced to physics and chemistry.»

as creatine phosphate when a phosphate group is eliminated, and muscles contain about five times more of this molecule than ATP. Based on these observations, Meyerhof and Lohmann concluded that the function of creatine phosphate in the muscle is medium-term energy storage, because when a phosphate group splits off ATP during muscle contraction, creatine phosphate can compensate for this loss by transferring a phosphate group to adenosine diphosphate (ADP), turning it back into ATP.

The formation of ATP by the transfer of a phosphate group from an energy-rich chemical compound to ADP plays a decisive role in more than just muscular contraction: it is one of the two fundamental means the cell has for storing energy. The other one is when the cell stores up, outside the cell membrane, a reserve of ions that it can allow to flow in as required. This also generates energy that can be used to produce ATP.

The important physiological concept of phosphate group transfer is also involved in the breakdown of sugars, such as glucose. Biochemists use the term glycolysis to denote the multi-phase breakdown of glucose, for which the cell requires no oxygen. After Otto Meyerhof and Karl Lohmann moved to the newly founded Kaiser Wilhelm Institute for Medical Research in Heidel-

berg in 1930, they devoted most of their work to elucidating this process. They discovered 6 of the 15 enzymes that convert molecules in this reaction sequence, and identified about a third of all intermediate products.

Two further scientists working in other locations made significant contributions to glycolysis research: Gustav Emden at Goethe University Frankfurt and Jakub Parnas in Lvov, Poland. As a result, the metabolic process is known as the "Emden-Meyerhof-Parnas pathway." The cell can use its end product, pyruvate, in many ways, for example as a raw material for the formation of lactic acid. In this way, glycolysis brought Meyerhof back to the beginnings of his physiological research.

The productive working relationship between Lohmann and Meyerhof came to an abrupt end due to the changed political circumstances of Nazi Germany. On November 16, 1935, Meyerhof received a letter from Baden's Minister for Culture, which read: "In reply to your letter of November 15, I wish to inform you that the question of the maintenance of your honorary professorship has now been decided in the light of yesterday's implementing regulation in the negative."

Even though Meyerhof's situation in Heidelberg deteriorated rapidly through the withdrawal of his teaching license, he remained at his institute for another two and a half years. In 1938, with no improvement in sight, he fled with his wife and son to Switzerland. The family eventually made it via France and Spain to the US, where Meyerhof was granted a professorship in Philadelphia. There he died of a heart attack in 1951 at the age of 67.

In Germany, Meyerhof's achievements long remained in the shadow of his friend and former teacher Otto Warburg, until the biochemist was newly recognized in 2001 through the creation of the Otto Meyerhof Center for Outpatient Care and Clinical Research at Heidelberg University.

In 1937, Karl Lohmann was called to Humboldt University in Berlin, where he headed the Physiology and Chemistry Institute for 14 years. In 1952 he moved to the Biochemistry Institute at the Medical & Biological Research Center of the German Academy of Sciences, where he continued to work even after his official retirement in 1964. In Berlin, his opportunities for conducting research were far more limited than in Heidelberg, and he devoted himself more to lecturing. For decades, Karl Lohmann, who would remain apolitical his entire life, represented the star biochemist of communist East Germany. The man who discovered the "energy cash of living cells," yet always kept a low profile, passed away on April 22, 1978.