History of Science

DOI: 10.1002/anie.200702929

Karl Lohmann and the Discovery of ATP

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adenosine triphosphate · history of science · Lohmann, Karl

"Scientific research is the one Olympic competition which awards Gold Medals only. To be second means being last", says Carl Djerassi, one of those unlucky scientists. He succeeded in synthesizing the pregnancy hormone progesterone and paved the way to the formulation of "The Pill". The Pill and its "father" were never distinguished by a Nobel Prize.

The list of those left out is long, perhaps longer than could be beneficial for the prize of all prizes. Our topic in this Essay is not the injustices though, but rather a curiosity—a scientific breakthrough, a truly fundamental discovery not honored with the Nobel Prize—the isolation and elucidation of the structure of ATP by Karl Lohmann.

We don't mean to criticize the Nobel Prize, nor the mode by which it is awarded, nor the committees involved. Rather we would like to discuss why an undoubtedly great discovery was passed over. Prize bashing in the case of the Nobel Prize is by far less suitable than for any other awards. The mere numbers render a just award impossible: In some years there are several worthy scientific accomplishments, but unfortunately, for each field there is only one prize per year (which can be shared by a maximum of three persons).

As to scientific breakthroughs not recognized with a Nobel Prize, medical science is hit hardest. Not only is the definition of the field vague—a prize is awarded for Physiology *or* Medicine—but of the two alternatives, the first is undoubtedly favored. Moreover, although tremendous progress in surgical procedures, for example, in cardiology or oncology, is saving thousands of lives per year, these areas are held in low esteem in Stockholm and are perhaps judged as "crafts" rather than intellectual accomplishments. But even when topics of theory are involved, physiology at its best, disturbing gaps are evident: There was never a Nobel Prize for the proof that DNA is the carrier of hereditary traits; the discovery of the fundamental principle of allosterism was not honored with the Prize. Chemists can also list examples of oversight: Didn't the 1,3-dipolar cycloaddition, now in the focus again in connection with "click chemistry", deserve the Prize? What about the rearrangement in cation chemistry that bears the name of its discoverer and is an essential tool in all modern synthetic laboratories?

The Discovery of ATP—The Most Important Accomplishment in Biochemistry without a Nobel Prize?

We won't discuss physics, literature, peace (especially fraught with false decisions), or even mathematics, which was excluded by Alfred Nobel from the beginning. Let us turn our attention instead to Karl Lohmann, to this quiet researcher who never uttered bitter words about his lack of Nobel Prize. One of us (P.L.), who was a graduate student in his research group in Berlin-Buch, confirms this from many years of personal contact. Karl Lohmann never even mentioned the great discovery of his epoch.

In 1929 Lohmann isolated ATP, adenosine triphosphate, from muscle and liver extracts.[1] Actually, Justus von Liebig had first isolated the compound, he referred to it as "inosinic acid", the deamination product of the adenine nucleotide, 80 years earlier from meat extracts.

The elucidation of the structure, initially controversial, was in close competition with Fiske and Subarrow.[2] Lohmann succeeded through acid hydrolysis of the colorless substance which provided two moles of phosphoric acid, one mole of adenine, and one mole of D-ribose-5-phosphate.[3] The correct structure of adenosine-5′-triphosphate was finally confirmed 20 years later by Alexander Todd, in due style: by chemical synthesis.[4]

Life's Energy Reservoir

Synthesis of the acid anhydride ATP requires energy, which can be recovered by hydrolysis of the compound. Thus ATP is the chemical energy reservoir per se—this and all the rest is textbook knowledge and will not be summarized here. But how could it be that this truly fundamental discovery did not receive the honor of a Nobel Prize? Let us look into the course of Lohmann's scientific life. There we might find some hints; we shall not be able to present a secured explanation.

Karl Lohmann was born April 10, 1898, in the northern German town of Bielefeld. His father was a farmer in the province of Westphalia. In World War I he served as an artillerist on the "west front". After the war he studied chemistry in Münster and Göttingen. In 1924 he obtained his doctorate degree with a thesis entitled (translated from German) "Chemical Investigations of the

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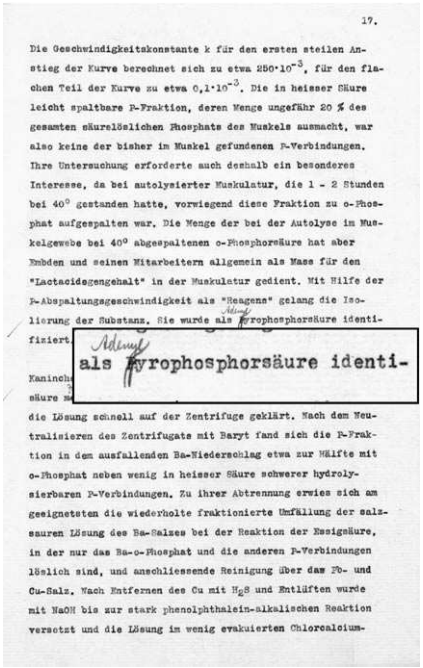
Montan Ore (Montanerz)", completed in Windaus's institute. (Later, in 1935 in Heidelberg, he completed his second doctorate, this time in medicine). In 1924 he also applied for a position with Otto Meyerhof, then at the Kaiser Wilhelm Institute for Biology in Berlin-Dahlem. Two years previous, in 1922, Meyerhof was awarded the Nobel Prize in Physiology or Medicine for his work on the energetics of muscle contraction. Now the focus was on the molecules and mechanisms that transformed metabolism into the mechanical work of the muscle. The "vitalism" doctrine of the 19th century was about to be replaced by the scientifically founded "chemistry of life". Meyerhof was the leading protagonist in this development: with exact physical methods he introduced thermodynamics, and with precise quantitative analytics he added stoichiometry to physiology. Meyerhof had just discovered a large gap in the energetics of muscular work: Lactic acid originating from glycolysis (and the heat of neutralizing the acid) accounted only for about half the measured balance. Lohmann showed that the missing heat stems from hydrolysis of a phosphoric acid anhydride.

A Near-Fatal Detour

A mistake almost ruined everything: Lohmann, with his competitors Fiske and Subarrow hot on his heels,[2] had initially suspected that pyrophosphate was the conspicuous phosphoric acid anhydride. His first three publications on the subject were based on this assumption. In the archive of the Berlin Brandenburg Academy of Science and Humanities a copy of his "Habilitationsschrift" can be found, which he submitted in 1928 to obtain the "venia legendi" (literally "the right to teach", the German degree for would-be university professors). There again he writes exclusively about "pyrophosphate". At decisive passages, though, the prefix "adenyl" had been added in pencil to the typewritten text (Figure 1). Obviously the manuscript was prepared under time pressure and had to be revised to keep up with the latest findings in the lab!

At that time phosphoric acid esters and anhydrides—Lohmann's focus of interest—were of utmost importance to researchers. Carbohydrate phosphoric acid esters were discovered in the labs of Meyerhof and others to be key intermediates in glycolysis and glycogen metabolism, and were integrated in the well-known metabolic pathways and cycles. P. Eggleton and M. G. Eggleton,[5] and almost at the same time C. H. Fiske and Y. Subarrow,[6] just had described the two "phosphagens", creatine phosphate and arginine phosphate (These phosphates were to contribute to Lohmann's fame!). Pyrophosphate was thought to be attached noncovalently to proteins. Today we know that inorganic pyrophosphate occurs in cells in minute amounts at most. It was Lohmann who discovered the covalent (anhydrous) link of pyrophosphate to adenosine monophosphate (Figure 2). Instrumental to this discovery was an analytical method described in his "Habilitationsschrift", the title of which was (translated from German) "A Method to Determine and Identify Phosphoric Acid Compounds and Its Results Related to Muscle Physiology". The method was simple but effective. Lohmann measured the rate of hydrolysis under acidic conditions and then compared it to that of authentic compounds. If the half-lives of the reactions differed by at least one order of magnitude, he could analyze even mixtures of compounds. And in this way he came across the component he had initially thought to be pyrophosphate, but which at closer inspection turned out to be adenosine-5′-triphosphate, ATP. The reaction enthalpy of the hydrolysis was $\Delta H = -14.6\ \mathrm{kcal\,mol^{-1}}$, which reflects the high transfer potential for endergonic metabolic reactions.

ATP was recognized by Meyerhof and Lohmann as the universal energy reservoir of the cell. The term "energy-rich phospho compound" was coined only later, in 1941 by Fritz Lipmann. Since then, generations of students have referred carelessly to "energy-rich bonds" which they suspect to be the meaning of the symbol "~", not knowing that the reaction enthalpy does not originate from the anhydride bond itself but rather from the greater stability of the reaction products.



17.

Die Geschwindigkeitskonstante k für den ersten steilen Anstieg der Kurve berechnet sich zu etwa $250 \cdot 10^{-3}$, für den flachen Teil der Kurve zu etwa $0{,}1 \cdot 10^{-3}$. Die in heisser SÄure leicht spaltbare P-Fraktion, deren Menge ungefähr 20 % des gesamten säurelöslichen Phosphats des Muskels ausmacht, war also keine der bisher im Muskel gefundenen P-Verbindungen. Ihre Untersuchung erforderte auch deshalb ein besonderes Interesse, da bei autolysierter Muskulatur, die 1 - 2 Stunden bei 40° gestanden hatte, vorwiegend diese Fraktion zu o-Phosphat aufgespalten war. Die Menge der bei der Autolyse im Muskelgewebe bei 40° abgespaltenen o-PhosphorsÄure hat aber Embden und seinen Mitarbeitern allgemein als Mass für den "Lactacidegengehalt" in der Muskulatur gedient. Mit Hilfe der P-Abspaltungsgeschwindigkeit als "Reagens" gelang die Isolierung der Substanz. Sie wurde als Pyrophosphorsäure identifiziert.

Adenyl
als Pyrophosphorsäure identi-

Kaninch
säure
die Lösung schnell auf der Zentrifuge geklärt. Nach dem Neutralisieren des Zentrifugats mit Baryt fand sich die P-Fraktion in dem ausfallenden Ba-Niederschlag etwa zur Hälfte mit o-Phosphat neben wenig in heisser SÄure schwerer hydrolysierbaren P-Verbindungen. Zu ihrer Abtrennung erwies sich am geeignetsten die wiederholte fraktionierte Umfällung der salzsauren Lösung des Ba-Salzes bei der Reaktion der Essigsäure, in der nur das Ba-o-Phosphat und die anderen P-Verbindungen löslich sind, und anschliessende Reinigung über das Pb- und Cu-Salz. Nach Entfernen des Cu mit H_2S und Entlüften wurde mit NaOH bis zur stark phenolphthalein-alkalischen Reaktion versetzt und die Lösung im wenig evakuierten Chlorcalcium-

Figure 1. Excerpt from a manuscript of Karl Lohmann's *Habilitationsschrift*. The prefix "Adenyl" was pencilled in before "Pyrophosphorsäure". (Archive of the *Berlin-Brandenburgische Akademie der Wissenschaften*, estate of Karl Lohmann.)

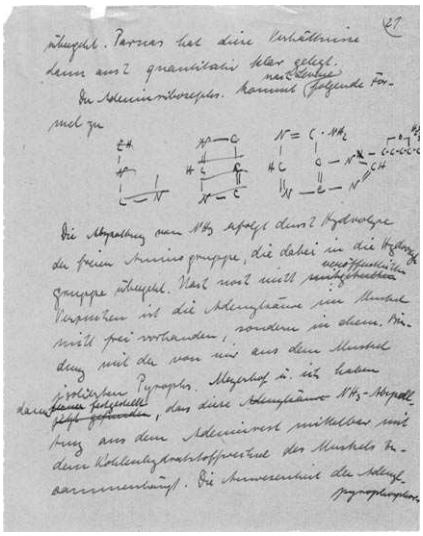


Figure 2. Formula of the "Adenosine Ribose Phosphate" from a handwritten manuscript, possibly a draft for a publication. (Archive of the *Berlin-Brandenburgische Akademie der Wissenschaften*, estate of Karl Lohmann.)

Right Time, Right Place

Lohmann's role in the discovery of ATP arose in part from serendipity. First of all he was at the right place at the right time. This period was the heyday for research on metabolic biochemistry, which was investigated at the highest level of quantitative precision in Meyerhof's institute, first in Berlin-Dahlem, and from 1929 on in the newly founded Kaiser Wilhelm Institute for Experimental Medicine in Heidelberg. Lohmann moved there as Meyerhof's head assistant. The other, perhaps even more important factor was the close cooperation of these two leaders of biology and chemistry favored by a deep personal friendship. Meyerhof's sharp philosophically trained mind supplemented in an ideal manner Lohmann's experimental skills. This may be one of the main reasons that Lohmann was not awarded the Nobel Prize in Physiology or Medicine for the discovery of ATP. He would have had to share it with Meyerhof, who had won it a few years previous for work in the same field.

Let us continue with Lohmann's curriculum vitae. His years in Heidelberg were his most productive. Lohmann was by no means one of those who succeeded only once with a great, albeit outstanding, discovery. In the field of pyrophosphates, he discovered "co-carboxylase", the coenzyme of the decarboxylases. He solved its structure and showed that it was the pyrophosphoric acid ester of thiamine; in other words, he elucidated the mechanistic link between a vitamin (B1) and energy metabolism. This discovery of fundamental importance alone would have deserved recognition. He showed the important role of Mg^{2+} in the enzymatic catalysis of phosphorylations. Above all, he found the reaction later named after him: the Lohmann Reaction. Muscle extracts contain high concentrations of creatine phosphate (the phosphagen mentioned above). This alone cannot support muscle contraction. Small catalytic quantities of ATP are sufficient to phosphorylate myosin, because ATP is continuously regenerated from creatine phosphate through transesterification. Apparently creatine phosphate is an intermediate energy reservoir.

Science and Politics

Meanwhile the National Socialists had wrested political control of Germany. Lohmann did not join the Nazi Party nor any of the other fascist organizations. He became a focus of attention for the regime anyway. The head of the Heidelberg academic staff pointed out that it would be advisable to take this excellent scientist away from Meyerhof, a Jew. This is why in 1937 Lohmann was promoted to professor of physiology in Heidelberg and in the same year in Berlin. Meyerhof emigrated in 1938, initially to Paris, then in 1940 to the USA. The Rockefeller Foundation endowed a chair for him at the University of Pennsylvania at Philadelphia, and there he died at the age of 67.

Researcher, Teacher, Administrator

The call to the Friedrich-Wilhelms-Universität zu Berlin (renamed in 1949 to Humboldt-Universität zu Berlin) deeply changed Lohmann's life. The cutting-edge researcher turned into an excellent university teacher and science administrator. He reformed curricula, organized lab courses, and drafted protocols for student experiments. Already in 1937 he had become director of the Institute of Physiology, and he held this post until fourteen years when later he handed it over to Samuel Mitja Rapoport, the most important biochemist of the German Democratic Republic.

Karl Lohmann survived two German dictatorships. Because of his flawless standing during the fascist period he became interim dean of medicine at the Wilhelms-Universität. He gave up this post soon, though, to return to his main calling as researcher and professor. In 1949 he was elected to the Academy of Sciences at Berlin (later renamed to Akademie der Wissenschaften der DDR, ADW). In 1950 he was elected Secretary of the Medical Section by unanimous vote and installed in this post by Prime Minister Grotewohl. In this second German dictatorship Lohmann was successful without compromising himself. He became vice director of the ADW Institute for Medicine in Berlin-Buch, and was the first director of the newly founded Institute for Medicine and Biology, also in Berlin-Buch. In 1957 he became President of the Institute for Nutrition in Potsdam-Rehbrücke (Figure 3). He was awarded many honors, (including the *DDR Vaterländische Verdienstorden in Gold*), was a member of important committees, was *Verdienter Wissenschaftler des Volkes*, founding president of the Society for Experimental Medicine, chairman of the *Biochemische Gesellschaft der DDR*, and council member of the International Union of Biochemistry (IUB)—all without being member of the communist party (Figure 4). He retired in 1964 and died in Berlin on April 22, 1978.

Returning to the question we asked at the beginning of this Essay: How

Figure 3. Karl Lohmann in an animated discussion.[7]

Figure 4. Karl Lohmann chatting with Otto Warburg at the Third Erythrocyte Symposium, November 1960, in the lecture hall of the Institute of Physiological and Biological Chemistry, Humboldt University, Berlin, Hessische Strasse 3–4.[7]

could it be that ATP and its discoverer went without a Nobel Prize? An unambiguous answer is not at hand. Likely it has to do with his mentor Otto Meyerhof, who was awarded the Prize for his work on the energetics of muscle contraction a few years before the discovery of ATP (1922, together with A. V. Hill). But other scientists have received two Nobel Prizes…

Maybe the answer is quite simple, as we mentioned above: Simply there are more great discoveries than Nobel Prizes! Lohmann's accomplishment is by no means lessened by the decision of the Nobel committee.

Received: July 2, 2007
Published online: January 22, 2008

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