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"Everything Now Seemed So Simple to Me …": Feodor Lynen (1911–1979), a Hero of Biochemistry

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Residual Material Saved from the Ruins

At the end of World War II, the city of Munich was mostly ruins. Many buildings of the university of the formerly flourishing Bavarian metropolitan city were destroyed, including the Chemical Institute. In April 1946, the Natural Science Faculty of the University of Munich was reopened. Feodor Lynen (Figure 1), Docent of Chemistry and head of the biochemical section at the institute of the Nobel laureate Heinrich Wieland, who carried out research into natural substances, was provisionally accommodated in the Institute of Zoology, which had remained undestroyed.[1] *"There were hardly any chemicals and glassware; as much as possible one improvised with the residual material saved from the ruins."*[2]

Figure 1. Feodor Lynen at his desk; no date given (Archives of the Max Planck Society, Berlin-Dahlem).

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The Chemistry Laboratory of the University of Munich had already been concerned with natural compounds before World War II. Since the 1930s, the Wieland laboratory had been investigating the oxidation of acetic acid in yeast cells. First hints concerning the special role of this compound had emerged at the beginning of the 20th century; Wieland's laboratory had already successfully proved that fatty acids and steroids must have been formed directly from acetic acid.[3]

Since his habilitation in 1941, Feodor Lynen had already been investigating, among other topics, the degradation of acetic acid by resuming an observation made by his thesis adviser Heinrich Wieland in 1938: Yeast cells were shaken with oxygen over several hours, thereby depleting their supply of oxidizable substances. If these cells were subsequently provided with acetic acid, they could oxidize it only after a certain period to produce energy through the citric acid cycle. This induction time could be shortened by the addition of oxidizable substances such as ethanol. Lynen concluded that, for the generation of energy, the yeast cells would first oxidize the ethanol added, and only thereafter would they transform the acetic acid added into the more reactive "activated acetate". His presumption, however, that this activated form was acetyl phosphate turned out to be wrong. Because of the war, he had to let this work rest at this stage for a number of years.

"Activated Acetic Acid"—a Thioester

When, after the end of the war, as Lynen reported, "*the scientific contact with the surrounding world had been re-established I got to know of the advances* (…). *The essential advance consisted in the notion that the newly-discovered, pantothenic acid containing coenzyme A participated in the formation of 'activated acetic acid' and that the 'activated acetic acid' was probably an acetylated coenzyme A*".[4]

Similarly, in the United States, the biochemist Fritz Lipmann had found out that he and Lynen were investigating similar areas. Furthermore, Lipmann was working in acetyl transfer reactions, and in 1947 discovered a new coenzyme, which, because of its acetyl group transfer properties, he had named acetyl coenzyme A. However, the chemical structure of the coenzyme was so complicated that the nature of the bond between the acetyl group and the coenzyme, as well as the mechanism of the acetyl transfer reaction were entirely unclear. Being an organic chemist, Lynen felt challenged to elucidate this chemical bond. In 1950, he described his influential idea for the solution of the problem in the following way: "*My brother-in-law, Theodor Wieland, was on holidays in his parents' house next to ours. He had (…) worked on pantothenic acid, the vitamin discovered by Lipmann to be a constituent of coenzyme A. We spent a whole night in shoptalk about the possible link between acetate and pantothenic acid but could not come to any conclusion. On my short way back (…) it suddenly came to my mind that the acetyl residue might be bound, not to pantothenic acid at all, but to sulfur. I recalled that in Lipmann's last paper on the composition of the purified coenzyme A preparations he had mentioned the presence of sulfur, but he did not pay much attention to it (…). In addition, it was known that all enzymatic reactions studied in which coenzyme A was involved required the addition of glutathione or cysteine, presumably as agents for the binding of inhibitory heavy metals. Third, as a chemist I knew that sulfhydryl groups are more acidic than hydroxyl groups, which means that acetic acid bound to sulfur must have the properties of an acid anhydride and this should have the capacity to acetylate amines or alcohols. The crucial step for me was that I put the three things together. I became very excited, hurried into my study, and looked into the 'Beilstein'. Soon I found that thioacetic acid was known to react with aniline to form acetanilide. I thus became completely convinced that 'activated acetate' must be a thioester.*" Lynen subsequently had his laboratory isolate acetyl coenzyme A from a boiled yeast extract. "*In two months' time this goal was reached, and in comparison with a synthetic thioester (…) it could be proved that my prediction was correct*". "*This whole story was most exciting*", Lynen remembered later, "*but it was to become even more dramatic when my short publication was sent to 'Angewandte Chemie' to be published in the December issue.*[5] *Everything now seemed so simple to me that I could hardly believe that nobody else (…) could have had the same idea (…). I was relieved only when I heard by letter from Otto Meyerhof and Carl Neuberg that my paper had come to the biochemists in the United States like a bombshell,*"[6] as Lynen's publication, Lipmann reported, "*filled a vacuum we had left open (…). Lynen also had the delicate chemical discrimination to recognize the properties of the acetyl bond as those of a thioester. They thus made sense of our finding a lot of -SH in purified CoA preparations which we had shoved under the carpet because our thoughts were fixed on pantothenic acid or phosphate as presumptive attachers*".[7] The interest in Lynen's publication was gigantic. With his discovery he was proven as an excellent biochemist, whose work elicited worldwide attention in the pertinent scientific circles.

Bernd Hamprecht worked as a chemical technician before studying chemistry at the Stuttgart Institute of Technology and the University of Munich. His doctoral thesis work on the regulation of cholesterol synthesis in rat liver was carried out in the laboratory of Feodor Lynen at the Institute of Biochemistry, University of Munich (1965–68). After postdoctoral work with Feodor Lynen (1968–70) and Marshall Nirenberg at the NIH (Bethesda, USA) as stipendiate of the Max Planck Society (1970–72), he became head of an independent research group at the Max Planck Institute for Biochemistry, Martinsried (1973–78). Subsequently he was Chair of Physiological Chemistry at the Universities of Wuerzburg (1978–85) and Tuebingen (1985–2008). Since 2007 he is Emeritus Professor at the Interfaculty Institute for Biochemistry, University of Tuebingen.

Heike Will studied pharmacy at the University of Wuerzburg and obtained her license to practice pharmacy in 1992. In 2004 she started doctoral studies of history of pharmacy/medicine at the University of Wuerzburg (awarded 2009) on the "Comparison of medicinal indications mentioned in the 'small distillation book' by Hieronymus Brunschwig (Straßburg 1500) with currently verified indications". From 2006–2009 she was awarded a scholarship from the Max Planck Institute of Biochemistry, Munich, for composing Feodor Lynen's biography. Since 2009 she has worked as research assistant at 'Forschergruppe Klostermedizin' Würzburg.

An Oasis of Decency

Scientists now also wanted to meet Lynen personally and invited him to the USA to attend a "Gordon Research Conference". Such an invitation to a German scientist was by no means matter of fact, even six years after World War II—many Jewish (bio)chemists, among them renowned scientists such as Otto Meyerhof or Carl Neuberg, and promising young scientists such as Konrad Bloch or Fritz Lipmann, had been driven into emigration during the Nazi period. At the Natural Science Faculty of the University of Munich, the political situation had remained comparatively quiet. Many of the scientists working there had hardly concealed their resentments against Nazism, such as Heinrich Wieland who had made it possible for a number of "non-Arian hybrid students" to study at his institute. One of his protégées, Hildegard Hamm-Brücher, later a prominent liberal politician in the Federal Republic of Germany, remembers her thesis adviser: "*He neither endangered his life by conspirative activities nor by death-contemning conduct*", but he had always "*proven himself as an example of integrity and civil courage and endeavored to preserve the chemical institute as an oasis of decency.*"[8]

Fatherless Adolescence

Joining the Nazi party (NSDAP; National Socialist German Workers' Party) was out of question for Lynen. Fe had a conservative influence from his family background—his family had been successfully engaged in the production of brass in the Aachen region for many centuries. Eventually his father broke the family tradition and accepted a professorship of machine engineering in Munich. Feodor Lynen was born on April 6th 1911 as the seventh of nine children. Financially well-equipped with a heritage from his grandmother's side, his family had an impressive house erected in the Munich suburb of Nymphenburg. In 1918, one of the Lynen brothers died in the war, and only two years later his father succumbed to a heart condition.

In 1930, Feodor Lynen started his studies of chemistry at the famous Chemical Institute of the University of Munich. However, he had to interrupt his studies in 1932: the ambitious student contracted a complicated fracture of his knee joint in a skiing race (Figure 2). He spent eleven months in hospital, and it was only in 1933 that he could continue his studies with a stiffened left knee. He became acquainted with his fellow student Theodor Wieland, son of the head of the institute, with whom he was soon connected in cordial friendship. He also became acquainted with the Wieland family, whose unconventional intellectual atmosphere impressed Lynen very much. It was not long after that he fell in love with Wieland's 19 year old daughter Eva and that the two of them became a couple. In 1937 Feodor Lynen and Eva Wieland married; five children, born between 1938 and 1946, emerged from this marriage.

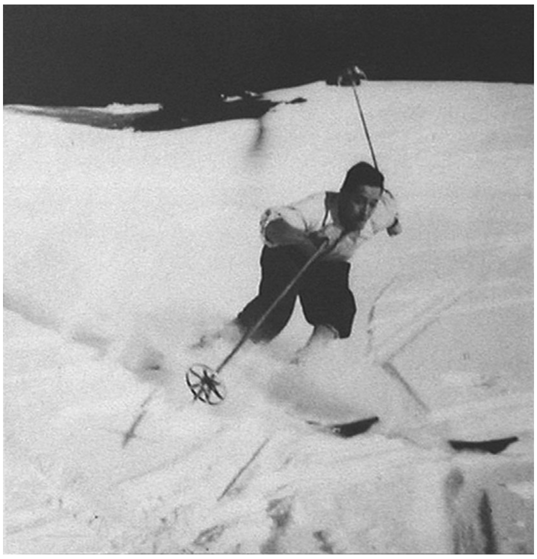

Figure 2. The student Feodor Lynen skiing at the Stolzenberg near Lake Spitzing, Bavarian Alps, approximately 1931. (From the private collection of AnneMarie Lynen.)

Not Concerned by the Denazification Law

Lynen's limp saved him from being drafted to the otherwise almost inevitable Nazi services such as the SA (Sturmabteilung) or also the army. Despite not being a member of the NSDAP, Lynen was appointed Docent of Chemistry in 1942, although "*only with concern*".[9]

After the end of the war and reopening of the Chemical Institute in 1946, Feodor Lynen received the information that the "law for the liberation from National Socialism" did not apply to him and that he was allowed to stay in his position as a docent. For Lynen it was now an urgent concern to reestablish contact with the displaced Jewish biochemists; soon enough he conducted a regular exchange of letters with Konrad Bloch and Carl Neuberg in the USA, and also with Fritz Lipmann, with whom samples of substances were also exchanged.

Another complicated leg fracture meant that Lynen could only take up the invitation to the United States in 1953, where he collaborated as a guest scientist in the laboratories of several colleagues for five months. Not politically charged, the German visitor was received cordially everywhere; several friendships, some of them life-long, with researchers in the US were formed here, including that with Fritz Lipmann, who was honored with the Nobel Prize in the same year. Obviously Lynen himself had hoped to receive this distinction, since in his congratulation letter to Fritz Lipmann he wrote: "*Well, you were just the more successful one! If I can really sincerely share your joy of receiving this unique distinction then this is partially due to my stay in Boston. I parted with a feeling of friendship for you and this has stayed this way.*"[10]

Nobel Prize 1964

Eleven years later, Lynen would eventually receive the Nobel Prize for Physiology or Medicine in Stockholm, together with Konrad Bloch, for his work on the "*mechanism and regulation of cholesterol and fatty acid metabolism*" (Figure 3). During these years, Lynen's research conditions improved significantly. In 1947, he was appointed as the first tenured Extraordinarius for biochemistry in the Natural Sciences Faculty at a German University, and in 1953 as Ordinarius (full professor). With this appointment, the still young discipline had taken a first step into independence, as this subject had always only been represented in medical faculties at German universities. An exception had been the Kaiser Wilhelm Society, later the Max Planck Society, in which correspondingly committed institutes had already been

Figure 3. Awarding of the Nobel Prize in Stockholm, 1964: The Swedish king congratulates Konrad Bloch, with Feodor Lynen on the right watching the scene. Lynen's wife Eva (third from left) and their three daughters Susanne, AnneMarie, and Eva-Maria are in the first row of spectators (Archives of the Max Planck Society, Berlin-Dahlem).

established for outstanding biochemists. Furthermore, Lynen had been provided with such a research facility, from 1954 on first within the "German Research Institution for Psychiatry" in Munich and two years later as director of the now independent "Max Planck Institute for Cell Chemistry", eventually, from 1972, in one of the newly erected buildings of the Max Planck Institute for Biochemistry in Martinsried on the outskirts of Munich (Figure 4). In this position, Lynen was always skilful enough to turn upcoming possibilities into objects for negotiation and to utilize them for his science.

Figure 4. Feodor Lynen, 1973 (Archives of the Max Planck Society, Berlin-Dahlem).

Lynen's research work led to the question of how fatty acids were oxidatively degraded. Here he introduced, in a way entirely unconventional at that time, simple model compounds and this way was able to detect the enzymes that participate in the degradation of fatty acids, later also called the Lynen spiral.[11] With this, a bridge became established for the understanding of the connection between the oxidation of fatty acids and carbohydrates, earlier designated as "combustion of fatty acids in the fire of carbohydrates"; this work was only made possible because of Lynen's elucidation of the thioester structure of the active coenzyme A derivatives, which also participated in this process.

For the pathway of fatty acid biosynthesis, Lynen had first presumed a mere reversal of these individual enzymatic steps. However, soon he had to recognize that he had been wrong. Again with the aid of simple model compounds, he succeeded in demonstrating that in the metabolism of yeast cells, which Lynen frequently used as "experimental animals", it was not individual enzyme molecules that were responsible for fatty acid synthesis but a tightly compacted complex made up from several discrete enzymes. Lynen describes the procedure in an illustrating way: "*One best does justice to the multienzyme complex (…) if one compares it with the assembly halls of industry. In both cases the individual parts introduced from outside are assembled piece by piece (…) and are only released from the factory site as a completed end product*".[12]

In the investigation of the individual steps of fatty acid biosynthesis, the direct participation of the vitamin biotin, which was one of the few vitamins that had not been investigated at that time, became obvious. Lynen succeeded in elucidating its mode of action and its participation in fatty acid biosynthesis: the natural construction of the fatty acid chains proceeds through a preceding carboxylation of acetyl-CoA, the product of which he designated "activated activated acetic acid" because of its energetic advantages.

The activated acetic acid also plays an important role in the biosynthesis of the terpenes, of which cholesterol is a member, and which soon came into Lynen's focus. It was indeed known that in the generation of the C5 building block common to all terpenes "*are combining three molecules of acetic acid, in the form of acetyl-CoA; but its chemical structure and the way of its formation from acetyl-CoA are lying in the dark still*", as Lynen wrote in 1957.[13] Lynen's discovery of the thioester also constituted the basis for understanding this sequence of reactions, since also in this instance the reactivity of the participating molecules, gained by the combination with coenzyme A, comes into effect. Finally, in isopentenyl pyrophosphate, Lynen and Bloch independently found a hitherto unknown intermediate in the biosynthesis of cholesterol. Lynen succeeded in providing proof for the identity of this compound with the sought-after basal unit of active isoprene.[14] With this result, the deciphering of the biosynthetic pathway of all terpenes had become possible. Lynen repeatedly raised the question of the physiological reaction mechanism; thus, for example, he succeeded in establishing the pacemaker function in cholesterol biosynthesis of the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase.[15]

Lynen always saw his basic research amalgamated into society to gain new insight in the causes of diseases with the aim to be able to develop new medications—an aspect that the Nobel Committee also had specially emphasized in its decision. Likewise it was important for Lynen to accept responsibility in public offices as, for example, the presidency of the Alexander von Humboldt Foundation. Many high distinctions were offered to him: honorary doctoral degrees, the Grand Cross of Merit of the Federal Republic of Germany, or the election into the order "Pour le Mérite", all of which filled him with great pride.

In 1979, the year of his routine dismissal from public service, Lynen underwent an aneurism operation. At first, this procedure appeared to be successful. Some days later, however, an intestinal icterus developed; in the following weeks all efforts of treatment proved unsuccessful. Feodor Lynen died on August 6, 1979.

What Remains?

For Lynen, the close connection with Heinrich Wieland had always been an important aspect of his life. He had experienced as strongly defining "*to get to know as a young person in the house of my father-in-law very many significant natural scientists (…) these were personalities of very great simplicity (…) and such things then leave their traces behind.*"[16]

Feodor Lynen's profound scientific education with Wieland and his personal qualities such as perseverance, readiness for risk, a superior ambition, and deep confidence in his own capabilities enabled him to very successfully carry out research, even under the conceivably adverse external conditions of the postwar period. As biochemistry in Germany had been isolated during the Nazi period, Lynen's excellent scientific work, his political integrity, and last but not least his aura of joy in life opened the gate to international science again. He created a scientific school that encompasses scientists from almost all continents who are or were working in leading positions in academia, research institutions, and industry.[17] Lynen's scientific insights have become part of general biochemical knowledge. In his commemoration, the Alexander von Humboldt Foundation established a research stipend named after Lynen, and every year the German Biochemical Society (GBM, "Gesellschaft für Biochemie und Molekularbiologie") distinguishes, on the occasion of the international meeting "Mosbacher Kolloquium" excellent scientists with an honorific lecture, the Feodor Lynen Lecture.

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[1] The present article contains passages from H. Will, *Sei naiv und mach' ein Experiment. Feodor Lynen. Biographie des Münchner Biochemikers und Nobelpreisträgers (Be Naive and Make an Experiment. Biography of Feodor Lynen, the Biochemist and Nobel Laureate from Munich)*, Wiley-VCH, Weinheim, **2011**.
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