The Great **Experimenter**

Life is chemical fluctuation – this is the view that shaped the research of Munich-born biochemist **Feodor Lynen**, who would have celebrated his 100th birthday this year. In clarifying the structure of "activated acetic acid," he laid the foundations for understanding the many processes of formation and breakdown in the cell, and for the study of such diseases as diabetes and arteriosclerosis. Lynen, a Director at the **Max Planck Institute for Cellular Chemistry**, was awarded the Nobel Prize in 1964 for his work on cholesterol and fatty acid metabolism.

TEXT **ELKE MAIER**

The article that appeared in the journal Angewandte Chemie in 1951 was short and to the point, not more than a page long. The molecule it described, in contrast, was so complex that scientists had spent years puzzling over what it might look like. The author, Feodor Lynen, had finally done it: he had put the pieces of the jigsaw together in the right combination to reveal the structure of acetyl coenzyme A, otherwise known as activated acetic acid – a compound that plays a key role in cell metabolism.

Feodor Felix Konrad Lynen was born in Munich's Schwabing district on April 6, 1911, the seventh child of a professor of mechanical engineering. Affectionately known as "Fitzi," he showed an active interest in chemistry from an early age, carrying out experiments in the attic of his parents' villa. After "making holes in his Sunday best trousers and an explosion resulting in slight injuries to his face and hands," he put his experiments temporarily on hold until he began to study chemistry at Munich University in 1930.

In the early 1930s, Munich was a stronghold of organic chemistry. Famous names such as Justus von Liebig, Adolf von Baeyer and Richard Willstätter had taught and conducted their research there. The range of topics was broad; scientists studied not only the structure of natural substances, but also the chemical conversions that took place within living cells. In the lab of the man who would be his father-in-law, Heinrich Wieland, the 1927 Nobel laureate, Lynen did his Ph.D. "On the Toxic Substances in Amanita" before turning his attention to a more digestible subject – brewer's yeast *(Saccharomyces cerevisiae)*, which he procured from Munich's Löwenbräu brewery.

Using radioactively marked compounds, Heinrich Wieland investigated the metabolic processes in the yeast. This easy-to-handle model organism is eminently suitable for clarifying biochemical questions. Wieland was particularly interested in the fate of acetic acid, a very simple organic molecule consisting of just two carbon atoms: a methyl group (CH_3) and a carboxyl group (CO_2H).

As the scientists of the day already knew, acetic acid plays a central role in metabolism: it is produced when carbohydrates, fats and proteins are burned, and is also a component of various biomolecules, such as vitamins, cholesterol and hormones. What they did not know was how the chemical reactions occurred, given that acetic acid is, by nature, slow to react. It must first be activated – and that was the crux of the matter – before it will convert anything at all.

Lynen, too, became captivated by "activated acetic acid" since, in his view, "the processes of life [offer] the most fascinating problems for a chemist." And so his interest turned initially to converting acetic acid into citric acid – the reaction at the center of the aerobic breakdown of carbohydrates.

Heinrich Wieland had made an interesting observation in this respect: he shook yeast cells together with oxygen for many hours, which used up all the usable (oxidizable) substances. If acetic acid was then added to "depleted" yeast of this kind, only after several hours could it be oxidized and thus used to produce energy.

But what exactly happened inside the reaction vessels? Feodor Lynen initially postulated that the acetic acid got its energy boost through phosphorylation – the addition of a phosphate group. Yet his experiments with acetic acid and inorganic phosphate ended in disappointment every time: the reaction mixture contained not a drop of citric acid.

The master in his element: Experimentation was the key to success for Feodor Lynen.

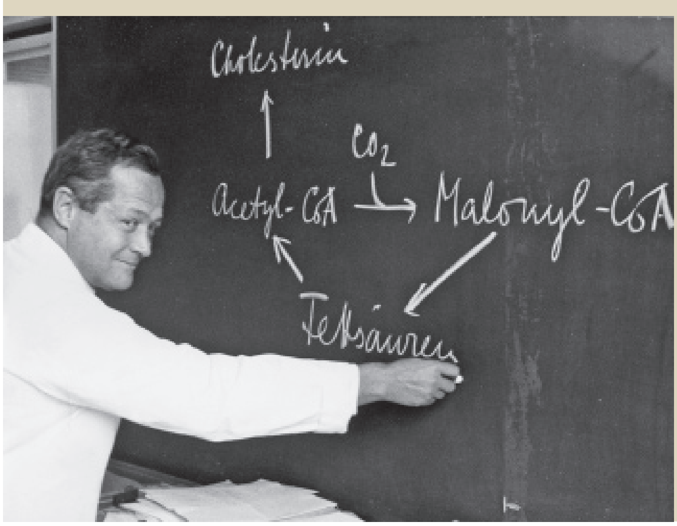
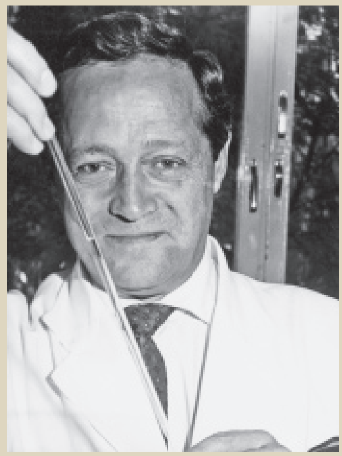


Photo: Archive of the Max Planck Society, Dahlem, Berlin

Many years went by before this problem was resolved. The initial spark came from a discovery made by biochemist Franz Lipmann, who was working in the US. He had isolated a previously unknown coenzyme from pigeon-liver extract in 1947. Since it was capable of transferring acetyl groups (the remains of acetic acid), he named it coenzyme A. It contained pantothenic acid, adenosine, phosphate and sulfur, and was directly involved in acetylation reactions – an indication that the acetylated form of this coenzyme may conceal the portentous "activated acetic acid." However, the structure of the compound was so complicated that it was not apparent how the acetyl was bound to the coenzyme.

The memorable moment when he discovered the answer was later described by Lynen in the following terms: "My brother-in-law, Theodor Wieland, was spending the holidays at his parents' house, which is next door to our house. He had been […] working on pantothenic acid, the vitamin that Lipmann had recognized as a component of coenzyme A. We spent the whole night discussing how acetate and pantothenic acid could be bound to each other, but we did not reach a solution. On my short walk back to our garden it occurred to me that the residual acetate may be bound, not to the pantothenic acid, but to the sulfur."



At the heart of (metabolic) events: Feodor Lynen and acetyl-CoA, "activated acetic acid." The picture was taken in October 1964, just a few weeks before Lynen was awarded the Nobel Prize.

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»However, hopes remain as yet unfulfilled that knowledge of cholesterol synthesis would enable us to find a way of controlling it with medication, thus cheating arteriosclerosis. But the guilty conscience that strikes many of us when we once again spread the butter too thick conceals the name of the Nobel Prize winner.«

Experiments with acetyl coenzyme A from the boiled extract of yeast proved Lynen right. Within two months he had confirmed his presumption experimentally, and then he immediately put his findings down on paper. But he had a nail-biting wait until they were published in Angewandte Chemie. "It all seemed so simple to me now, I could hardly believe that no one would have the same idea in the intervening period," reported Lynen.

At the time, numerous research groups were working on the problem of "activated acetic acid." Would someone beat him to it at the last minute? In the end, what followed was the news that his "disclosure had hit the biochemists in the US like a bomb." The publication had struck Fritz Lipmann "without warning".

His clarification of the structure of "activated acetic acid" brought Feodor Lynen international recognition. From then on, his career took a steep upward trajectory. In 1953 he was appointed the first professor of biochemistry at a German university. The following year he assumed the directorship of the Institute of Cellular Chemistry that had been specially established for him within the Max Planck Society. The institute later merged with the Max Planck Institute of Biochemistry in Martinsried, near Munich. In 1964, Feodor Lynen won the Nobel Prize, together with Konrad Bloch, for his discovery of the "mechanism and regulation of the metabolism of cholesterol and fatty acids."

"I am happy in my job, but I have never let it become an obsession. I have always taken the time to enjoy life," said Lynen of himself. He demanded absolute top performance from his people, as he did from himself, but working with him also promised a measure of fun away from the lab bench. In the collection of essays entitled *Die aktivierte Essigsäure und ihre Folgen* ("activated acetic acid and its consequences") that was published to mark his 65th birthday, former members of his team wrote contributions on the subject of "Feodor Lynen and I."

The contributions tell of relentless lab work, often late into the night, and Lynen's dreaded visits to the lab to keep up to speed on the latest findings – or lack of them: "You great lump!", "Well, you great artist?", "You can throw that right away!" – the boss's comments "caused people to go either ashen white or beet red in the face, depending on their temperament."

But they also recall the ski trips and hiking expeditions they all took in the Alps, the Mardi Gras holidays, the garden parties in Starnberg and sociable gatherings at the Augustiner beer garden or at Oktoberfest (where, incidentally, Lynen also corrected a doctoral thesis or two). Just like in the lab, it definitely did not go down well if you tried to steal away early on such occasions: "You just sit right back down there. Don't be so boring!" he would say in his thick Bavarian accent.

Feodor Lynen never had any intention of founding a school, yet that is exactly what he did. In the 37 years he taught, 88 undergraduates and doctoral students worked in his labs, and there were post docs and guest scientists as well. Many of his students were later appointed professors at universities or Max Planck Institutes. The "Lynen school" soon had offshoots all around the world.

Experiments lay at the heart of Lynen's work. He did not think much of extensive literature studies, pure theory or wild speculation. "Nature is always unpredictable, and the only way to tackle a biochemical problem is to do experiments," was his belief. But even he did not always find the answer in a test tube – sometimes it came to him on the way to the garden.