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FRITZ ALBERT LIPMANN  
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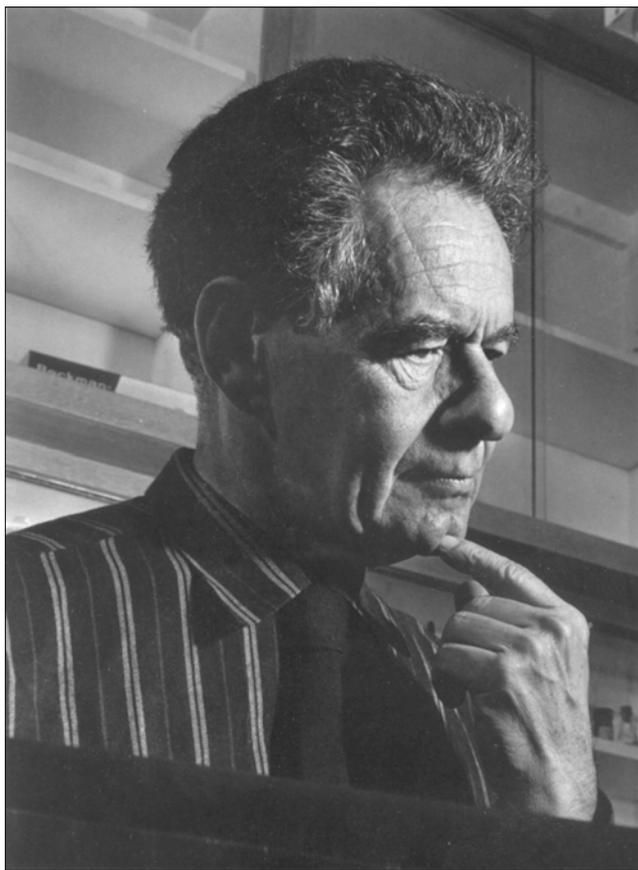
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*A Biographical Memoir by*  
WILLIAM P. JENCKS  
AND  
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*Fritz Lipmann*

# FRITZ ALBERT LIPMANN

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BY WILLIAM P. JENCKS AND  
RICHARD V. WOLFENDEN

**F**RITZ LIPMANN WAS LARGELY responsible for identifying and characterizing the connection between metabolism and the energetics of living systems that makes life possible.

## EARLY LIFE AND EDUCATION

Lipmann was born at the end of the nineteenth century, on 12 June 1899, in Königsberg, which was then the capital of East Prussia. Königsberg was close to the Russian border, and the German government provided more support to the university than might have been expected for a city of its size. Königsberg later became part of the USSR and was renamed Kaliningrad. It was one of the Hanseatic cities and contained a harbour that was connected by a sound to the Baltic Sea. The Lipmann family regularly spent the summer there, close to the seashore. The taxis were droschkes, horse-drawn carriages. Lipmann remembered a visit of the Kaiser, who was driven through the town in a carriage with four horses and a coachman with a plumed helmet.

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Lipmann attended the Gymnasium in Königsberg, where he studied, among other subjects, both Latin and Greek—he preferred Latin. He was not an outstanding student at the Gymnasium, nor later at the university. His father was a lawyer, who told his son that he “was not enough of a crook to be an outstanding lawyer.”

An uncle, who was one of Lipmann’s heroes, died young from a ruptured appendix. This was one of the experiences that led him to study medicine in Munich in 1917. In 1918, he was called up into the army and assigned to the medical service. He had a short experience with the study of military medicine, close to the front lines, before the war ended in 1919. When he returned to Königsberg, he encountered the ravages of the influenza epidemic. In spite of months of contact with patients, he did not become infected.

After the war, in 1919, he joined his brother Heinz in Munich and studied medicine for a semester. His brother was interested in literature, the theatre and poetry. Fritz spent much of his time with the very active community of artists and writers at that time in Schwabing, the Greenwich Village of Germany. He was also close to Friedel Sebba, a painter who also had a strong interest in the theatre. During that period, he never ventured scientifically outside the confines of medicine, and later regretted not having gone to hear the great chemist Wilstätter.

His parents and friends suggested that he study pathology, to prepare for a career in the practice of medicine. He spent three months dissecting cadavers and examining slides. This led him to choose a different direction for his career. He enrolled in a remarkable three-month course in biochemistry that was taught by Peter Rona, who had worked with Leonor Michaelis. Rona taught three Nobel prizewinners: E.B. (later Sir Ernst) Chain, Hans (later Sir Hans) Krebs and Lipmann. This was an unusual step for a

physician at that time, when biochemistry was considered a mere adjunct to physiology, but Lipmann was an unusual physician. He characterized this course as a kind of “bio-chemical marathon.”

In 1923, inflation was raging in Germany, and the political situation was deteriorating. He accepted a fellowship to visit the pharmacology laboratory of Laqueur in Amsterdam. During this crucial four month period, he decided that he wanted to be a biochemist, and that it was essential to learn chemistry. Later, in 1924, he published a paper with Rona on colloid chemistry (1924), which was accepted as his thesis for the MD degree from the University of Berlin, and two papers with J. Planelles on the effects of injection of glucose, glycogen and starch on the levels of blood sugar in rabbits (1924[2], 1925).

To obtain a clearer understanding of chemistry, Lipmann attended a lecture course in chemistry given by Hans Meerwein, a leading organic chemist at the Kaiser-Wilhelm Institute for Biology in Berlin. This stimulated him to study chemistry with Meerwein, and he was awarded the doctorate three years later, in 1927.

However, his main interest was in intermediary metabolism and biochemistry so that, with support from his father, he spent three years in the laboratory of Otto Meyerhof in one of the Kaiser-Wilhelm institutes (now the Max-Planck institutes) in the Dahlem neighborhood of Berlin. The late 1920s were a remarkable time in Dahlem. Other investigators in Meyerhof's laboratory included Karl Lohmann, who discovered Adenosine Triphosphate (ATP), and Karl Meyer, Severo Ochoa, Dean Burk and David Nachmansohn. Erwin Negelein, Hans Gaffron, Walter Christian and Hans Krebs worked in the laboratory of Otto Warburg, who was on the top floor and seldom descended into the lower regions. Nevertheless, his influence permeated the institute. There

was constant contact with Neuberg's biochemistry institute and with Otto Hahn and Liese Meitner in the chemistry institute where they discovered nuclear fission.

Hill and Meyerhof had demonstrated a quantitative relationship between muscle contraction and lactic acid formation from glycolysis. Lipmann showed that creatine phosphate was cleaved during muscle contraction, although he did not establish its role conclusively (1927). Meyerhof, in turn, had been greatly influenced by Otto Warburg. Lipmann never worked directly with Warburg, but was certainly influenced by him. François Chapeville had lunch with Warburg at a meeting in Paris and mentioned that he had worked with Lipmann. Warburg replied, "Ah, then you are my grandson." Lipmann became interested in the metabolic effects of the fluoride ion, which was known to inhibit muscle contraction. He confirmed that fluoride inhibits glycolysis and reacts with methaemoglobin to form a fluoro-methaemoglobin. Fluoride also inhibits liver esterase (1930[1], 1929[2]). Three papers describing this work and the work in Meyerhof's laboratory resulted in the award of the PhD degree in 1929, under the sponsorship of Carl Neuberg (1929[2], 1930[2], 1941).

In the same year he met Freda Hall, whom he later married. Freda, or Elfried, was the daughter of Gertrud Hall. She was born in Defiance, Ohio, USA, on 19 December 1906 when her parents were in the USA; her father was a German businessman. The family returned to Europe and lived first in West Prussia and then in Berlin. She was talented in drawing and went to art school. Later, she worked as a fashion illustrator for newspapers. Lipmann met her in Berlin at the *Sozialistenball* in 1929.

Lipmann was involved in many activities outside of science. Berlin in the 1920s was a centre of artistic as well as scientific activities, and Lipmann had a strong interest in

paintings and in the theatre. His brother had moved to Berlin and was the dramatist with Leopold Jessner, the director of the Staatstheater. Lipmann described the people involved with the theatre as a "clan, closed up and agitated by their problems and intrigues." He noted that they included "unusual characters and beautiful women, often astonishingly intelligent, who were not unsimilar to scientists." He spent considerable time with painter Friedel Sebba, who had made a portrait of Lipmann and his brother Heinz in 1926.

#### ENERGY

Hill and Meyerhof had shown that there is a close relationship between the production of heat and the formation of lactic acid from glycolysis when muscles contract in the absence of oxygen. That relationship was assumed to be causal, until Einar Lundsgaard, working in Copenhagen, showed that muscle can still contract in the presence of iodoacetate, which blocks glycolysis so that lactate is not formed. When he injected iodoacetate into rats, the rats went into rigor and died after a few minutes. Looking for a source of energy for that contraction, he now found a parallel with the breakdown of creatine phosphate, a relationship that had not been observed in the absence of iodoacetate. Meyerhof's laboratory had shown that the hydrolysis of creatine phosphate releases a large amount of heat, very similar to that released by the hydrolysis of ATP. Lundsgaard realized that when glycolysis was blocked by iodoacetate, the energy released by the hydrolysis of creatine phosphate was used to provide the energy for contraction of the muscle. In Lipmann's last year in Meyerhof's laboratory, Lundsgaard joined the group, and Lipmann became involved in that work. Using platinum electrodes sealed into manometric vessels to stimulate muscle

preparations, he was able to demonstrate a quantitative relationship between creatine phosphate breakdown and contraction in intact muscle. It gradually became apparent that the creatine phosphate in muscle represented a reservoir of phosphoryl groups that could feed into ATP. It was found later that the energy released in glycolysis is used to form 1,3-diphosphoglyceric acid, phosphoenolpyruvate and creatine phosphate.

These compounds have very large and favourable Gibbs free energies of hydrolysis, comparable with that of ATP; they are “energy-rich” compounds that can provide the driving force for the synthesis of ATP, which in turn is used to provide the driving force for most of the energy-requiring reactions in all living systems.

Lipmann’s two-year fellowship for his work with Meyerhof could not be renewed. After searching with difficulty for his first paying job, he moved in 1930 to Albert Fischer’s laboratory in the Kaiser-Wilhelm Institute in Berlin to study cell growth in tissue culture. Here he was in close contact with K. Linderstrom-Lang, E. Lundsgaard, and H.M. Kalckar. The move to Berlin had the added advantage that he could more easily meet Freda Hall. In Fischer’s laboratory he developed a technique to measure the growth of cells in tissue culture by the manometric measurement of oxygen uptake by fibroblasts in Warburg vessels. The accumulation of carbon dioxide was prevented by the presence of potassium hydroxide in a side vessel. He was interested in the large amount of glycolysis that occurs in normal embryonic fibroblasts in the presence of air, which he found to be similar to that in malignant cells (1929[2]).

At the end of the first year, Fischer was invited to set up a new laboratory in Copenhagen, funded by the Rockefeller and Carlsberg Foundations. This was fortunate, because Hitler’s influence in Germany was increasing

rapidly and would soon result in the Holocaust. During the following year, Lipmann took advantage of a Rockefeller Foundation Fellowship to visit P.A. Levene's laboratory at the Rockefeller Institute for Medical Research. Before he left for New York, he and Freda Hall were married on 23 June 1931.

Lipmann asked Levene if he could work on the phosphate link in phosphoproteins because he thought that there might be an energy-rich linkage to nitrogen as in creatine phosphate. Instead, he encountered O-esterified phosphate in vitellic acid, a protein purified from egg yolk. From this material, of which it constitutes roughly 10%, he was able to isolate pure serine phosphate, which, unlike other phosphoryl compounds that were then known, was quite stable to hydrolysis in strong acid. The common occurrence of serine-bound phosphate in tissue proteins, especially from brain, was to remain mysterious for many years, until E.R. Sutherland's much later discovery that cyclic adenosine monophosphate (AMP) acts as a "second messenger" for many hormones by stimulating enzymes that phosphorylate specific receptors. Lipmann later expressed some regret at having stumbled on this gold mine unwittingly, and having passed it by.

In the summer of 1932 he joined the many other scientists who traveled by boat to the Marine Biological Laboratory at Woods Hole on Cape Cod in Massachusetts, and worked in the rooms of Leonor Michaelis. There he made friends with Linderstrom-Lang before returning to the new institute in Copenhagen.

In Copenhagen, Lipmann began by working on the Pasteur effect, the first regulatory reaction in biochemistry to attract attention. Pasteur had shown that yeast cells, which can grow in the presence or absence of air, suppress the anaerobic production of alcohol when air is present. The

same effect is observed in fibroblasts, muscle and brain, resulting in much more effective production of useful energy from glucose. He tried in vain to observe a direct effect of oxygen or of redox indicators on the glycolytic enzymes. Many years later it became apparent that the ATP:ADP (adenosine diphosphate) ratio, rather than oxygen itself, is the agent that regulates the activity of some glycolytic enzymes.

A new direction of his research developed in 1937 as he began to investigate the oxidation of pyruvate by a strain of *Lactobacillus delbrueckii*. Preparations from this organism were found to contain two cofactors: thiamine pyrophosphate and flavin adenine dinucleotide. A more important observation was that the reaction proceeded only in the presence of inorganic phosphate. Unlike the glycolytic enzymes of yeast, the components of this system resisted solubilization, because its mitochondrial nature was unknown. However, when isotopically labeled phosphate and adenylic acid were added to this preparation, the oxidation of pyruvate led to the production of ATP from ADP and phosphate. This is now known as oxidative phosphorylation, the primary source of readily usable energy in aerobic organisms. This work was performed while Lipmann was still in Copenhagen, and was presented in 1939 at the 7th Cold Spring Harbor Symposium on Long Island, New York.

This work was conducted under the shadow of the rapid growth of fascism and anti-Semitism in Germany; Lipmann's Danish friends warned him of the danger of remaining in Denmark. For advice, he contacted Dean Burk, a colleague from Meyerhof's laboratory who had visited the Lipmanns in Denmark and shared an interest in the Pasteur effect. Burk was moving to Vincent du Vigneaud's laboratory in the Cornell Medical School at New York Hospital in Manhattan, and had two openings in his laboratory. Lipmann

had been strongly recommended to du Vigneaud by Linderstrom-Lang. He invited Lipmann to join the laboratory, and the invitation was accepted. Du Vigneaud was awarded the Nobel Prize later, in 1955, for determining the structures of the peptide hormones oxytocin and vasopressin.

In New York, Lipmann encountered Rollin Hotchkiss, who was working with René Dubos at the adjacent Rockefeller Institute. Hotchkiss had isolated tyrocidin and gramicidin, the first bacterial antibiotics, from *Bacillus brevis*; Lipmann showed that these antibiotics contain several non-protein D-amino acids, by analysing their hydrolysates with D-amino acid oxidase.

#### THE APPEARANCE OF THE SQUIGGLE

In the spring of 1940, the Lipmanns vacationed in Vermont, where Fritz meditated on the significance of activated phosphate compounds such as ATP and acetyl phosphate. It was known that deuterium-labelled acetate was incorporated into fatty acids, steroids and amino acids, and Lipmann had shown that acetyl phosphate was formed from ATP and acetate in bacterial extracts.

It was at this time that he wrote his famous paper "The metabolic generation and utilization of phosphate bond energy" (1941) for *Advances in Enzymology*, introducing the squiggle ( $\sim$ P) for "energy-rich phosphate," which provides the driving force for many biochemical reactions and processes. These include physical processes such as the contraction of muscles, the transport of ions and other molecules across membranes, and chemical reactions for the biosynthesis of proteins, nucleic acids and other large molecules.

In spite of this impressive record of accomplishments, it was difficult for Lipmann to obtain a stable position in research or teaching. He attributed some of this difficulty

to a lack of experience in preparing lectures. A particularly harrowing experience took place at a widely attended symposium at Madison, Wisconsin, in 1940 on intermediary metabolism. He had been asked to give a talk on the Pasteur effect, in which by then he had little interest. The lecture he had prepared was much too long, and he had time to deliver only half of what he had prepared before Carl Neuberg, the chairman of the session, was forced to stop him. The audience was uncomfortable, and word of this event contributed to his later difficulty in finding a decent position. Lipmann was finally awarded a Ciba Fellowship in the Department of Surgery at the Massachusetts General Hospital in Boston, which was chaired by Edward Churchill. His research was supported by a grant obtained by Oliver Cope, a surgeon who was interested in endocrinology and basic research. It is a credit to the flexibility of the medical and scientific community in the USA that it was possible to make such an appointment in a department of surgery.

The importance of his paper on activated phosphate compounds as a source of readily available energy was recognized quickly, and soon a number of biochemists came to work in his laboratory. He received financial support for his research from the Commonwealth Fund and was able to support a remarkably capable technician, Constance Tuttle, who worked with him for many years.

He isolated an enzyme from pigeon liver that permitted colorimetric determination of the acetylation of sulphonamides and other aromatic amides in the presence of ATP and acetate. He expected that ATP would react with acetate to give acetyl phosphate, which would then acetylate the sulphonamide. Indeed, the enzyme did catalyse the acetylation in the presence of ATP and acetate. However,

acetyl phosphate, the presumed intermediate in the reaction, was inactive as an acetylating agent.

The crude liver extract that was active for acetylation by ATP and acetate lost its activity rapidly, but the addition of boiled liver extract gave full reactivation. This indicated that the extract contained a heat-stable cofactor that is required for acetylation. Lipmann, N.O. Kaplan and G.D. Novelli purified the liver extract and obtained a compound that contained a thiol group and adenylic acid.

Roger Williams, the discoverer of pantothenic acid, and Beverly Guinard hydrolysed the cofactor and showed that it contained  $\alpha$ -alanine and adenylic acid in equivalent amounts. Lipmann's group then used alkaline phosphatase and an enzyme obtained from an extract of liver to cleave the compound and obtained pantothenic acid. At approximately the same time, D. Nachmansohn and John, and W.S. Feldberg and Mann, found a cofactor in an extract from brain that activated the acetylation of choline by ATP and acetate. Lipmann's group found the same activity in a dialysate of brain extracts and named it coenzyme A (now abbreviated to CoA); the A stood for the activation of acetate. It contained a thiol group, but the function of this group was not immediately apparent. E.E. Snell and his co-workers identified the compound as part of a cofactor required by *Lactobacillus bulgaricus* and showed that it was a peptide containing pantothenic acid and mercaptoethanol. F. Lynen and P. Reichart isolated acetyl-CoA and showed that the acetyl group is a thiol ester, and "energy-rich" compound containing a reactive acetyl group. J. Baddiley and his co-workers synthesized pantetheine 4'-phosphate and showed that it was converted to CoA by reaction with ATP. Kaplan showed that the third phosphate group of CoA is on the 3' position of the ribose with a phosphatase from rye grass

that is specific for cleavage of a phosphate ester at that position. This confirmed the complete structure of CoA.

Further investigation in Lipmann's and other laboratories soon showed that acetyl-CoA and other thiol esters of CoA function as acyl donors in many synthetic and metabolic pathways. In the citric acid, or Krebs, cycle, acetyl-CoA adds an acetyl group to oxaloacetate to give citrate. The large sulfur atom of CoA has only a weak overlap with the carbonyl group, so that the acidity of the acetyl moiety of acetyl-CoA is similar to that of a ketone. The acetyl group can therefore lose a proton easily to give the enolate, which then adds to the ketonic carbonyl group of oxaloacetate to give citrate and free CoA. Although citrate itself is a symmetrical molecule, the reaction was shown to be stereospecific by labelling the acetyl-CoA.

In 1953 Lipmann summarized this and other important work on the structure and function of CoA and its acyl derivatives in a comprehensive review (1953) that included descriptions of the role of acyl-CoA thioesters in the synthesis of fatty acids and steroids, as well as the acylation of arylamines and of acetyl-CoA itself, in acetoacetate synthesis. David Novelli, Nathan Kaplan and Mary Ellen Jones played especially important roles in the laboratory, as senior investigators who provided advice and help to others.

In the same year, Lipmann became a Nobel laureate in Medicine and Physiology, with Hans Krebs. Acetyl-CoA provided the crucial link in the citric acid cycle that had been conceived by Krebs, foreshadowing a similar role for carbamyl phosphate in the urea cycle that Lipmann was to discover.

At the time that he received this recognition, Lipmann's work on CoA had reached what he considered the 'mopping up' stage. His work had been supported generously

for some time by the National Institutes of Health, and the National Science Foundation offered him an additional five-year grant that allowed more latitude for exploration. He felt that there was broad scope for progress in the recognition that  $\sim P$  was acting as a kind of energy quantum in biological systems, which could be used in many other areas of metabolic function and biosynthesis.

#### CARBAMATE AND SULPHATE ACTIVATION, AND PROTEIN SYNTHESIS

He next turned his attention to carbamyl transfer, by which urea derivatives were formed, presumably from a substituted carbamic acid. Microbial extracts had been shown to catalyse the breakdown of citrulline in the presence of phosphate, leading to the inference that carbamyl phosphate might serve as a precursor in the synthesis of citrulline. Seeing a possible resemblance between acetyl phosphate and carbamyl phosphate, he set out with Mary Ellen Jones to look for carbamyl phosphate in extracts of *Streptococcus faecalis* that catalysed the cleavage of citrulline in the presence of phosphate. They obtained a product that was more stable to acid than acetyl phosphate, whereas carbamyl phosphate had been expected to be less stable. However, Leonard Spector, then associated with Paul Zamecnik in a neighbouring laboratory, was able to perform the first effective synthesis of this material by analogy with the synthesis of acetyl phosphate by the reaction of inorganic phosphate with ketene. Carbamyl phosphate, generated by the reaction of potassium cyanate with inorganic phosphate, was thus identified as the material that Jones had isolated, and was then tested for activity in microbial and human preparations. In a short communication to the *Journal of the American Chemical Society*, Jones, Spector and Lipmann reported (1955) that ATP could be generated by the reaction of carbamyl phosphate with ADP, and was converted

quantitatively to citrulline in the presence of bacterial extracts. They also described a somewhat slower reaction with aspartate to generate carbamyl aspartate, the first step in the biosynthesis of uridine and cytidine derivatives.

The combination of cyanate with inorganic phosphate attracted Lipmann's attention as one of several reactions by which the first biological molecules could have been formed, leading to the spontaneous formation of a form of  $\sim P$ , interconvertible with the anhydride bonds in ATP. However, he regarded polymeric anhydrides of phosphoric acid as more likely to have served as the primary phosphoryl donors in early organisms. Lipmann once remarked that, in his experience, people's interest in the origin of life tended to increase with advancing age; he maintained a detached air of levity in discussing an area so inaccessible to experiment.

Sulphate esters occur widely in nature, particularly in the ground substance of cartilage, chondroitin sulphate, and in cerebroside. The activation of sulphate was already known from R.H. DeMeio's work (DeMeio et al., 1955) to require ATP, but no anhydride of phosphoric and sulphuric acids had been described in the chemical literature. Helmuth Hilz observed formation of a phosphate-sulphate compound with release of pyrophosphate from ATP. Further experiments by Philip Robbins showed that the actual donor of sulphate in biosynthesis is not, as might be expected, a simple anhydride of sulphate and AMP: that compound is formed enzymically in preparations from rat liver, but was found to be inactive as a sulphate donor. Instead, a second molecule of ATP is required to generate adenosine-3'-phosphate-5'-phosphosulphate, which serves as the general donor of sulphate in enzyme reactions. The first reaction, in which a sulphate-phosphate anhydride bond is formed by the attack of sulphate on ATP, was shown to be quite

unfavourable energetically. The second ATP-consuming reaction, however, is energetically favourable, so that the overall energy balance is nearly zero for the formation of 'active sulphate'. These two reactions are catalysed by distinct enzymes.

Protein synthesis presented a much greater challenge because of its complexity, but Lipmann had predicted in 1951 that it would proceed by activation of the carboxyl groups of amino acids. Mahlon Hoagland, working in Zamecnik's laboratory, demonstrated the existence of amino-acid-activating enzymes in rat liver, and showed that the action of these enzymes resulted in cleavage of ATP to pyrophosphate, which was consistent with formation of amino-acid-AMP anhydrides similar to the anhydrides that had been shown by Paul Berg to be formed during acetate activation. Lipmann's laboratory became involved when Earl Davie and William Koningsberger isolated the tryptophan-activating enzyme and showed that it was specific for that amino acid.

From the faithfulness with which amino acid sequences were known to be expressed, it was evident that a major part of the puzzle was missing. Francis Crick suggested that the principle of base-pairing would be found to be involved in protein synthesis, in which each amino acid might be equipped with a polynucleotide "adapter" carrying an anti-codon for that amino acid. Hoagland and Holley soon confirmed, independently, that a nucleic acid was indeed part of each amino-acid-activating system. Expecting at first that a phosphate-amino-acid anhydride might be involved, the Lipmann group showed by treatment with ribonuclease that an adenosine derivative containing the amino acid was released, indicating that it must be esterified at the 2' or 3'-terminal adenosine of tRNA. Efforts to determine the site of attachment revealed that the amino acid isomerizes between these positions with a half-time of a few millisec-

onds under physiological conditions. The generality of the adaptor hypothesis gained important support from experiments by von Ehrenstein in the Lipmann laboratory showing that tRNA from bacteria could be used in haemoglobin synthesis in reticulocytes, and from François Chapeville's demonstration that alanyl-tRNA, prepared from cysteinyl-tRNA by treatment with Raney nickel, incorporated alanine in place of cysteine in systems directed by poly(UG), which codes for cysteine.

Between 1961 and 1964, Daniel Nathans and Jorge Allende separated soluble factors from the supernatant fluid of disrupted *E. coli* that brought about the incorporation of many amino acids from tRNA into protein simultaneously in the presence of mRNA and ribosomes, using GTP as an energy source. The GTP requirement of these elongation factors seemed difficult to understand in view of the energy available in the amino acid ester linkage to tRNA. Through the use of puromycin, an antibiotic that resembles the terminal adenosine residue of tRNA and can participate in some of its reactions, Anne-Louise Haenni and Jean Lucas-Lennard showed that GTP hydrolysis leads to translocation of peptidyl-tRNA from an acceptor site to a donor site, where it stands ready to transfer its peptide to the next incoming amino acyl-tRNA. These experiments defined the chemical steps in protein synthesis as they are understood today. The role of GTP in mediating mechanical events in microtubules and other cellular processes was foreshadowed by these experiments on peptide elongation.

Lipmann maintained an active laboratory during his later years at the Rockefeller University. Providing a counterpoint to the machinery for protein synthesis, he showed that cyclic peptide antibiotics such as gramicidin and tyrocidine are synthesized by the sequential addition of amino acids on polyanzymes. He returned to another of his early

interests in studying the phosphorylation and sulphation of tyrosine residues in proteins as a result of transformation, and showed that a phosphotyrosine residue produced by the action of an oncogene-encoded tyrosine kinase was energy-rich.

In an autobiographical collection of essays and scientific papers, entitled *Wanderings of a biochemist* (1971), Lipmann describes his early years of learning and wandering, and the process of following one's instinct without knowing exactly where it will lead. His instinct was remarkable, and few parts of biochemistry were not advanced by the results of his work. Lipmann died on 24 July 1986, at the age of eighty-seven, not long after having learned that his latest research grant application had been successful.

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