Obituaries

Fritz Lipmann (1899–1986): an appreciation

Fritz Lipmann, one of the most influential biochemists of the 20th century, died aged 87 on 24 July 1986 in Poughkeepsie, New York, after a short illness. Since 1969, he had been professor emeritus at The Rockefeller University, although he preferred to omit 'emeritus'. Best known for introducing the concept of high energy or energy rich bonds in metabolism, which he denoted with the 'squiggle', as in ~P, he was the first scientist to enunciate the principle that ATP serves as the common currency of energy exchange in metabolism. Dr Lipmann received the Nobel Prize for Physiology or Medicine in 1953 for the discovery and identification of coenzyme A.

Early training and scientific work

Fritz Lipmann was born in Koenigsberg, Germany, in 1899 (the city is now Russian and known as Kaliningrad). After completing his high school studies in 1917, he studied medicine in Koenigsberg, Munich and Berlin. He recalled that his scholastic achievements both in school and at the university were only average. His medical studies were interrupted for about a year in 1918 when he served as a military medical assistant and gained considerable experience in what would now be termed emergency medicine. Lipmann commented in later years that he was told by a sergeant that he would never amount to anything. His early work in biochemistry was done as a medical student under the tutelage of Peter Rona (an early associate of Leonor Michaelis) in Berlin. The resulting work on colloid chemistry was used for his MD thesis and became the subject for his first paper, published in *Biochemische Zeitschrift* in 1924. In 1923 he received a three-month fellowship to work with Ernst Laquer in the Department of Pharmacology in Amsterdam. It was there that he performed his first biochemical research, which prompted him to continue his studies in the biochemical sciences. He obtained his MD from the University of Berlin in 1924 and pursued a PhD in Chemistry, which he received in 1927 under the tutelage of Hans Meerwein in Koenigsberg and Otto Meyerhof at the Kaiser-Wilhelm Institute for Biology (now the Max Planck Institute) in Berlin. Even though Meyerhof was a Nobel Laureate, he was unable to sponsor a PhD student; Carl Neuberg in Berlin served as Lipmann's nominal graduate professor. After being awarded his PhD, Lipmann remained with Meyerhof's group, where he studied

phosphate ester chemistry with Karl Lohmann. The properties of hydrolysis of phosphate compounds by 1 N HCl were important in quantitating and characterizing ATP, creatine phosphate and various sugar phosphates. Otto Warburg's group was located at the same institute, and Hans A. Krebs was there with Warburg at the same time. Meyerhof accompanied by Lipmann, moved his institute to Heidelberg in 1930. Lipmann wrote that the time he spent with Meyerhof laid the foundations for all that he was to accomplish on his own.

Dr Lipmann took advantage of a Rockefeller Foundation fellowship and spent a year with P. A. Levene at The Rockefeller Institute for Medical Research (now Rockefeller University) in New York in 1931. Levene had just demonstrated that phosvitin, isolated from egg yolk, contained 10% phosphate by weight. Lipmann speculated that phosvitin might contain a high-energy storage form of phosphate (P~N), but he identified it as phosphoserine which was not energy-rich in nature. When Lipmann first elucidated the chemical properties of phosphorylated serine residues in the 1930s, no one could predict the importance that they have assumed today. Lipmann moved to Albert Fischer's laboratory at the Biological Institute of the Carlsberg Foundation in Copenhagen in 1932, and remained there until 1939, where he studied the Pasteur effect (inhibition of glucose consumption by oxygen) in fibroblasts in tissue culture. Prior to the advent of antibiotics, this methodology was fraught with difficulty and not as commonly used as it is today. An interest in the Pasteur effect prompted him to the study of the mechanism of pyruvate oxidation, thereby leading him to the discovery of acetyl phosphate, an energy-rich and activated form of phosphate (or acetate), in *Lactobacillus delbrueckii*. This work served as the background for his formulation of the concept of the high energy bond and prompted the line of work which eventually led to the discovery of coenzyme A.

Lipmann moved to Cornell University School of Medicine in 1939, where he worked in Vincent Du Vigneaud's department in the laboratory of Dean Burk (a former colleague in the Meyerhof laboratory). He compared the composition of amino acids with the D-configuration in tumorigenic and normal tissue and found no difference. Lipmann collaborated with Rollin D. Hotchkiss at the nearby Rockefeller Institute to show that the polypeptide antibiotics gramicidin S and tyrocidine contained amino acids of the D-configuration. The first volume of *Advances in Enzymology* (1941) contained Lipmann's famous review in which he discussed the role of the high energy bonds of ATP, creatine phosphate and phosphoenolpyruvate in metabolism. In his autobiography he described how he 'stepped into a hornet's nest' by using 'bond energy' to express the potential energy derivable from a bond instead of the generally accepted meaning of energy expended to form a bond. He also introduced the term 'group transfer potential' in this article as an alternative to high energy

bond and group activation In retrospect, the conflicts surrounding the terminology forced everyone to address the issues and may have accelerated the adoption of the concept

Later scientific work

Lipmann took a position as a Research Chemist in the Department of Surgery at the Massachusetts General Hospital in Boston in 1941 Up until this time he had done most of his own experimental work with some collaboration, moreover, he was the sole author on 35 of the 47 full papers he had then published In 1941, he supervised his first full-time technician (L Constance Tuttle), who was to be co-author on several subsequent publications During 1942–1943 he was joined by H A Barker, who was on sabbatical leave from the University of California This began the era of the discovery of active acetate as a derivative of coenzyme A (coenzyme of acetylation), resulting in our present awareness that coenzyme A plays a central role in the metabolism of all organisms

The number of students and postdoctoral fellows associated with Lipmann increased greatly during this work Nathan O Kaplan was the first postdoctoral associate to join him and G David Novelli was his first graduate student Earl R Stadtman, a graduate student with H A Barker, soon joined the laboratory as a postdoctoral fellow Other laboratories played an important role in work on the coenzyme A. Roger Williams, Beverley Guirard and Esmond Snell participated in the identification of pantothenic acid and pantetheine in the coenzyme Feodor Lynen showed that the acetyl group was attached to the coenzyme as a thioester forming a high energy bond (previously, most thought that the acetyl groups would be covalently linked to one of the phosphates of coenzyme A) Prior to Lipmann's identification of active acetate as acetyl coenzyme A, the mechanism of formation of citrate from oxaloacetate as postulated by Krebs was only a matter of conjecture The reaction of acetyl coenzyme A with oxaloacetate to yield citrate, first described by Severo Ochoa in 1949, represented a final piece of the puzzle regarding the citric acid cycle Lipmann was appointed professor of Biological Chemistry at Harvard Medical School in 1949 His last work on coenzyme A involved the discovery of the ATP-dependent citrate cleavage enzyme with Paul Srere When Lipmann received the Nobel Prize in 1953, which he shared with Krebs, he had already begun looking toward other problems

In contrast to the indirect routes and blind alleys which finally led to the discovery of coenzyme A, the elucidation of the nature of active carbamate as carbamoyl phosphate in 1955 came in a very direct and straightforward fashion

In 1957 Dr Lipmann moved to The Rockefeller University as professor where he worked on various aspects of ribosomal protein synthesis for 15 years He was greatly interested in the mechanism of amino acid activation by adenylation and the subsequent formation of charged transfer RNA This mechanism with the involvement of the pyrophosphate split, parallels acetate and fatty acid activation and this may have been part of the basis for his attraction toward this problem The resolution of bacterial elongation factors into Tu and Ts (unstable and stable) and G was a formidable problem The properties and mechanisms associated with the elongation factors also attracted his attention Francois Chapeville, working in Lipmann's laboratory, prepared [^{14}C]alanine-tRNA^{Cys} by reduction of [^{14}C]cysteine-tRNA^{Cys} In collaborative experiments with Seymour Benzer, it was demonstrated that the alanyl derivative was incorporated into hemoglobin in positions corresponding to cysteine This proved that the adaptor RNA was the important component in the placement of amino acids in the polypeptide chain and not the amino acid *per se*

Lipmann turned his attention to nonribosomal polypeptide biosynthesis in the late 1960s and facets of his earlier research returned to the forefront He first turned his attention to the mechanism of amino acid activation in gramicidin S biosynthesis which also involves the pyrophosphate split of ATP In this system, pantetheine serves to transfer the intermediates from site to site on a multienzyme complex Pantetheine also forms a part of the coenzyme A molecule Gramicidin S biosynthesis exhibited many parallels with both fatty acid and protein biosynthesis Subsequent studies focused on the biosynthesis of tyrocidine, linear gramicidins and valinomycin

Lipmann also worked on other projects over the years These include photophosphorylation and photosynthesis, protein kinases, muscle contraction, the mechanisms of regulation of transcription and translation in bacterial systems, guanosine tetraphosphate (magic spot) metabolism, mRNA capping, tyrosine phosphate in proteins and tyrosine sulfation in transformed cells

Scientific style

Lipmann was interested in principles of life's processes and worked with the most appropriate systems to address specific questions He tried to identify important problems and work toward their solution Some research inevitably led into blind alleys and many results were not of great importance He preferred, moreover, to work in areas which were not overcrowded with other investigators After the discovery of coenzyme A, for example, he left the field to let others do the 'mopping up' He initiated work on cyclic AMP in the late 1960s, soon thought that this area was becoming overcrowded, and subsequently devoted much less of his energy to this research

One of his favorite expressions was 'What is the mechanism?' He mapped out general areas of research and directions In later years he rarely designed a protocol, and left this task to the members of his laboratory When progress was being made, he wanted to be kept informed and continued to be excited and stimulated by the results When a project was not going well, he freely offered his suggestions for trying new approaches It was generally up to postdoctoral associates or graduate students to write the papers He might make a few changes, or he might completely re-write the manuscript He spent considerable time writing reviews on subjects of his interest or invited summaries for various books

On the basis of his achievements, he was unquestionably a biochemical genius How these achievements were made, however, differ from the expected characteristics of a scientist of such stature To begin with, he was either unwilling or unable to follow a complicated argument It was not unusual for him to state that he could not follow the logic of a seminar or a personal conversation When he wanted to understand a train of thought he asked question after question to get the speaker to make smaller and smaller steps between an observation and conclusion As a result of this much closer scrutiny, Lipmann might find that a conclusion was untenable I believe that this constant striving to simplify contributed to his success His curiosity and desire to learn also prompted him to ask many questions of a general nature, that might seem elementary for a first year graduate student This curiosity and enthusiasm never waned After understanding the background of a problem,

however, he was often able to make incisive comments or pose questions that helped to clarify ideas and concepts Nearly everyone who came into contact with him held high regard for his scientific intuition The source of this astuteness, however, might defy or transcend apparent logic

Lipmann wrote that he lacked the ability to make a good impression Although he spent considerable time preparing for various symposium talks, he was not a gifted speaker He was also ill at ease in answering questions after his seminars After contemplating a question for several days (or months), he might formulate a new line of experimentation which went further than any implications that the questioner might have originally had in mind Although his thought processes may have lacked speed, they certainly possessed undeniable power

Dr Lipmann had a long career in research Although he did not establish an independent laboratory until he was over 40 years old, more than 140 graduate students, postdoctoral associates, and visiting faculty performed research in his laboratory They occupy positions over the globe He prided himself that his best work was accomplished after the age of 40 against the adage that one's best work is performed at a young age Of course, he received many honors and awards of his outstanding achievements – too many to mention here I recommend the following reading list to those who wish to read more about this remarkable man

Autobiographical

Lipmann, F (1971) *Wanderings of a Biochemist*, Wiley-Interscience

Lipmann, F (1984) A long life in times of great upheaval *Annu Rev Biochem* 53, 1–33

Commemorative

Kaplan, N O and Kennedy, E P (1966) *Current Aspects of Biochemical Energetics*, Academic Press

Richter, D, ed (1974) *Lipmann Symposium Energy, Regulation and Biosynthesis in Molecular Biology*, Walter de Gruyter

Chapeville, F and Haenni, A-L eds (1980) *Concepts of Chemical Recognition in Biology*, Springer-Verlag

Ebashi, S ed (1985) *Cellular Regulation and Malignant Growth Lipmann Symposium*, Japan Scientific Societies Press

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Steve Prentis 1951–1987

Steve Prentis, who edited *TIBS* from 1978 until 1984, was killed in a car crash near Cold Spring Harbor, New York, on the last day of February 1987 The accident occurred after a party to celebrate the first issue of *Genes and Development*, Steve's latest journal

Steve would have been 36 on March 18th He was born in Coventry, England, but moved to Birmingham when very young and always considered himself a 'Brummie' He read chemistry at Warwick University and was proud of the 3rd class degree he obtained in 1972, claiming that a survey by the University Authorities had to be quietly suppressed when it proved an almost perfect inverse correlation between undergraduates' exam performance and success in later life Whatever the truth of this, there is no question about Steve's later performances He went from strength to strength and had shown no signs of slowing down when fate so cruelly cut short his progress

After a couple of short-lived jobs in industry (one as a technical editor), he landed a job as a Desk Editor with *FEBS Letters* He had applied for the job only as a means of getting to Amsterdam to visit a friend, and his amazement at getting the job was matched only by that of his mother 'But Steve, how can you work in publishing? You can't spell and your handwriting is terrible '

Steve returned to England in 1976 to become an Assistant Editor of the *Brewer's Guardian*, a job with strong appeal for a man who enjoyed his pint! He must have cemented his taste for seeing his words in print as well, for from then on he was always keen to write, whether

filling the baleful slot on the front page of *TIBS* as the publication deadline loomed, or producing his highly successful book, *Biotechnology* But it is not so much as a writer that his friends and colleagues will remember Steve, but as a peculiarly successful editor with an easy style and warm nature

In 1978, Steve returned to Elsevier, when he was appointed Staff Editor of *TIBS* in Cambridge, England Already a successful journal, Steve's excellent partnership with the second Editor-in-Chief, John Tooze, greatly expanded its recognition and its circulation On one occasion, checking up on an advisory session he had had with John Tooze, Steve telephoned to clarify contacts' names and areas of interest John had no problem until it came to Steve's final query. 'Who is this chap S V Forté?' Tooze racked his brains for a few moments until the penny dropped 'Steve' he said, 'You're fired!'

Steve was the perfect man to deal with the sometimes competing demands of the giant co-publishers, Elsevier and the IUB *TIBS* always came first It was never quite clear how he managed in the early days when his office was a small windowless room above an off-licence He was surrounded by endless cups of coffee, rapidly filling ash trays and mountains of unreviewable biochemical symposia proceedings Out of this seeming chaos emerged a magazine that consistently informed and entertained an increasing number of the world's biochemists As his contacts widened, his reputation for sensible fair dealing grew, along with his sense of what was important in biochemistry and molecular biology. Much of the expansion of the publication programme of Elsevier Cambridge was due to Steve's enthusiasm and/or on his direct initiative In 1983, he started *Trends in Biotechnology* and in 1985, *Trends in Genetics*, which he endowed with an impressive board of editorial advisors It was not surprising that his qualities attracted J D Watson as he searched for someone to take over as Director of Publications and Head of the Banbury Centre at Cold Spring Harbor, nor surprising that having taken the job, Steve immediately started a new journal!

Steve Prentis was universally liked and respected, which was the secret of his success He was creative, innovative and above all a great communicator An excellent listener, he consulted widely before taking decisions, but the decisions were always his own His humour was inexhaustible, and his balance between the serious business and the funny side of things was so well judged that he was always fun to work with, yet he never caused offence through indiscretion or taking sides He will be sorely missed

JUDITH HALL and TIM HUNT