In memory of Professor Leonor Michaelis in Nagoya: Great contributions to biochemistry in Japan in the first half of the 20th century

Toshiharu (Toshi) Nagatsu

Research Institute of Environmental Medicine, Nagoya University, Furo-cho, Chikusa-ku, Nagoya, Aichi 464-8601, Japan
Fujita Health University School of Medicine, 1-98 Dengakugakubo, Kutsukake-cho, Toyoake, Aichi 470-1192, Japan

Abstract

Leonor Michaelis spent the years of 1922–1926 as Professor of Biochemistry of the Aichi Medical College (now Graduate School of Medicine, Nagoya University) in Nagoya, Japan. Michaelis succeeded in gathering many bright young biochemists from all over Japan into his laboratory, and made tremendous contributions to the promotion of biochemistry in Japan. Michaelis was invited to present lectures over those years. Kunio Yagi, who was Professor of Biochemistry at Nagoya University in the second half of the 20th century, succeeded in crystallizing the “Michaelis” enzyme–substrate complex. Historically, Michels has had an enormous impact on biochemistry in Japan.

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1. Introduction

Leonor Michaelis (1875–1949; Figs. 1 and 2) spent the years of 1922–1926 as Professor of Biochemistry of the Aichi Medical College (now Graduate School of Medicine, Nagoya University) in Nagoya, Aichi, Japan. During that time Michaelis had an enormous impact on the development of biochemistry in Japan, prompting the establishment of the Japanese Biochemical Society in 1925.

On the occasion of celebrating the centenary of the publication of the famous paper by Michaelis and Menten in Biochemische Zeitschrift on the Michaelis theory of the enzyme–substrate complex in 1913 [1], I would like to present a historical overview of the tremendous contributions of Leonor Michaelis to the development of biochemistry in Japan in the first half of the 20th century.

Kunio Yagi [2,3], who later became Professor of Biochemistry of the School of Medicine at Nagoya University and was my mentor at the School of Medicine, followed the work of Leonor Michaelis and succeeded in crystallizing the “Michaelis” enzyme–substrate complex of \( \alpha \)-amino acid oxidase, confirming the hypothesis offered in the famous paper by Michaelis and Menten in 1913.

Kunio Yagi published a special monograph, “Professor Michaelis and Japan,” in 1973 [4], and also wrote a historical memoir of Michaelis in his manuscript in “New Horizons in Biological Chemistry” in 1980 [5].

The invitation for Michaelis to become Professor of Biochemistry at the Medical School in Nagoya was also mentioned in an autobiographical memoir of Michaelis in the NATIONAL ACADEMY OF SCIENCES, USA in 1958 [6].

During his stay in Nagoya, Michaelis was invited to present lectures in many places throughout Japan and also to organize highly stimulating special courses for young Japanese biochemists. A detailed story on lectures given by Michaelis in Sapporo, Hokkaido was recently reported by Fujita et al. in Japanese in the Journal: SEIKAGAKU (BIOCHEMISTRY) published by the Japanese Biochemical Society in November 2012 [7].

2. Invitation of Leonor Michaelis to Nagoya in 1922

The Department of Medical Chemistry at the Medical School in Nagoya had been settled in 1916 as the prototype of the present Department of Biochemistry at the School of Medicine at Nagoya University. On the occasion of having raised this medical school from a lower grade to university rank as the Aichi Medical College in Nagoya in 1920, then Governor Miyao of Aichi Prefecture hoped to introduce a centre of excellence to the College. President Yamazaki of the College consulted with Seizo Katsunuma, who was Professor of Internal Medicine at the College at that time and later became President of Nagoya University; and they decided to invite an internationally famous professor of biochemistry to the medical college. Shigeru Sakai, who was also Professor of Internal Medicine of the College, was in Europe during that period and also contributed to the invitation of Leonor Michaelis. As a result, with the
recommendation of Carl Neuberg, Professor of Biochemistry in Berlin, Germany, Leonor Michaelis received the invitation to become Professor of Biochemistry in Nagoya. Although such an invitation was an unusual event in Japan at that period, especially for a country with people speaking Japanese, a language completely different from Western languages and having a different (Oriental) culture, Michaelis kindly accepted the invitation and was appointed as Professor of Biochemistry at Aichi Medical College in Nagoya on October 30, 1922. Immediately after his acceptance, the Aichi Medical College in Nagoya started establishing a new Department of Biochemistry for Professor Leonor Michaelis with the best facilities at that time. Iwao Ogawa was appointed as the first research assistant of Leonor Michaelis. Ogawa had graduated from Tohoku University at Sendai, was a staff member of Nagoya Medical College at that time, and later became Professor and Director of the Research Institute of Environmental Medicine of Nagoya University, which was established by President Seizo Katsunuma in 1946. On November 1, 1922, Leonor Michaelis arrived at Kobe Harbour, Japan, where Ogawa welcomed him and guided him to Nagoya, travelling by train. President Yamazaki welcomed him at Nagoya Station. A gorgeous residence was provided for him on the school campus. On November 9, 1922 Michaelis went to Tokyo to meet with Sabro Kakiuchi, who was his friend and Professor of Biochemistry at the University of Tokyo and later became the founder of the Japanese Biochemical Society in 1925.

One hundred thousand Japanese yen at that time, several billion yen at the present value, was provided for supporting the newly established Biochemistry Department chaired by Michaelis as Professor. His salary was twice as much as that of President Yamazaki of Aichi Medical College. When Professor Michaelis came to Nagoya, he brought with him many documents, apparatuses, and drugs from Germany.

He served as Professor in the Department of Biochemistry, and its Director, for three and a half years until he left Nagoya in 1926, when he travelled to the United States, where he first went to Johns Hopkins University in Baltimore and later, in 1929, to the Rockefeller Institute in New York as Professor.

Leonor Michaelis came to Nagoya alone at first in 1922. When his wife, Hedwig Philippsthal Michaelis, and their two daughters, Ilse and Eva, came to Nagoya in 1923, the Michaelis family became complete, enjoying a comfortable family life (Fig. 3). Michaelis was not only an outstanding biochemist but also an excellent pianist. When Albert Einstein visited Japan in 1922, he visited Nagoya in December of that year. Michaelis invited Einstein to his house,
and both played in concert, the piano by Leonor Michaelis and the violin by Albert Einstein.

Kunio Yagi later wrote “Although most of the things (which Michaelis brought from Germany) were burnt during the Second World War, journals he brought still remained in the library attached to the Faculty” [5].

3. Crystallization of the “Michaelis” enzyme–substrate complex by Kunio Yagi [2,3]

Kunio Yagi was Professor of Biochemistry at the School of Medicine, Nagoya University, and served as President of International Union of Biochemistry and Molecular Biology (IUBMB) during 1994–1997. When he was a medical student at Nagoya University, he saw many items that had been brought there by Leonor Michaelis and still remained during the period of 1939–1942. Thus he was inspired to approach the nature of the hypothetical “Michaelis” enzyme–substrate complex. For that purpose he chose a flavoprotein, d-amino acid oxidase [d-amino acid: oxygen oxidoreductase (deaminating), EC 1.4.3.3] as a good tool, because its chromophore, FAD, when examined by its absorption and fluorescence spectra, was expected to be an indicator that would reveal the formation of a complex between an enzyme and its substrate [5]. His first major achievement was the crystallization of the enzyme–substrate complex model in 1960 [2,3]. The apoenzyme protein of d-amino acid oxidase was mixed with FAD and benzoic acid, which was regarded as a substrate substitute or pseudo-substrate, and crystals of the complex were obtained from an ammonium sulphate solution. Takayuki Ozawa, who later became Professor of Biochemistry at School of Medicine, Nagoya University, also contributed significantly to this famous study. This work was a historical landmark to prove the presence of the existence of the “Michaelis” enzyme–substrate complex.

4. Contributions of Leonor Michaelis to Biochemistry in Japan

Many excellent young biochemists were gathered into the Biochemistry Laboratory of Michaelis in Nagoya not only from all over Japan, from the northern district of Hokkaido to the southern district of Kyushu, but also from Korea. Many such young biochemists and students educated and trained by Michaelis later became leaders of biochemistry themselves (Figs. 3 and 4). Some of the names of those in his Laboratory were as following: Iwao Ogawa from Nagoya, as mentioned above; Akiji Fujita from Kyoto, who later became Professor of Biochemistry at Kyoto Prefectural Medical University; Kunio Dokan from the University of Tokyo; and Kaoru Daikoku from Sapporo. Kaoru Daikoku graduated from the

Fig. 5. Professor Leonor Michaelis in his Biochemistry Laboratory at Aichi Medical College in Nagoya.

Fig. 6. Professor Leonor Michaelis in his Biochemistry Laboratory with his research assistants and students at Aichi Medical College in Nagoya.
University of Tokyo and later became Professor of Biochemistry at Hokkaido University School of Medicine in Sapporo in 1922. He invited Michaelis to come from Nagoya to Sapporo, Hokkaido in 1925 to give some lectures at Hokkaido University; and he and his family had an intimate friendship with Michaelis and his family in Sapporo [4,7]. The lectures given by Michaelis in Japan were presented in German, and his assistants and medical students at Aichi Medical College worked hard to master German in order to understand his lectures (Fig. 4). They wrote their manuscripts published with Michaelis or by themselves in German under the guidance of Michaelis. The lectures by Michaelis were translated into Japanese by Ogawa and Daikoku, and their notes still remain at Nagoya University and Hokkaido University [4].

Michaelis was excellent in mathematics, physics, chemistry, and medicine, and also in several languages. He introduced physical chemistry into biology and medicine in his research and in his most advanced lectures in Japan. He was not only an outstanding biochemist, but also an excellent mentor. He did experiments by himself and also taught kindly and patiently many young biochemists how to perform experiments in his biochemistry laboratory (Figs. 5 and 6).

During his stay in Nagoya as Professor of Biochemistry, Michaelis wrote 11 papers by himself or with Japanese coworkers; and 20 papers were written by Japanese co-workers under his guidance [4]. For example, topics included a membrane specifically permeable to cations only, an extension of the theory and practice of potentiometric measurements, and an extension of the theory of pH [6].

5. Conclusions

Leonor Michaelis in Nagoya as Professor of Biochemistry at Aichi Medical College, presently known as the Graduate School of Medicine, Nagoya University, truly had an enormous impact on biochemistry in Japan, having introduced new concepts of physical chemistry into biology and medicine and raised many leaders of biochemistry in Japan in the early period of the development of biochemistry in the 20th century. He was an outstanding biochemist and an excellent teacher.

He will long be remembered for his great contributions to biochemistry in Japan.

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