International Journal of Pharmaceutics 418 (2011) 3–5

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Commentary

Takeru Higuchi, the man and the scientist

ARTICLE INFO

Keywords:
Higuchi
History

ABSTRACT

Madison (United States), December 7th 1941. It is early in the morning. Takeru Higuchi is listening to the radio when the programme is suddenly interrupted: part of the American naval fleet has just been destroyed in an air-raid on Pearl Harbour. For the United States, their involvement in the World War is now inevitable. For Takeru Higuchi, the son of Japanese immigrants, this was the beginning of an inner struggle. As a student of Physical Chemistry at the University of Wisconsin, he had received a fellowship from the American government; the war between the two countries pulled him in opposing directions. His austere childhood had left him with an extremely determined character and Takeru Higuchi chose to overcome his suffering by a personal dichotomy: he gave his heart to Japan but put his trust in the United States and devoted his energy to the service of science. This choice made him a man and a scientist of exceptional qualities, producing scientific work astonishing by its originality and quantity, making a major contribution to the pharmaceutical profession, particularly in the field of research.

Takeru Higuchi (1918–1987) was born on January 1st 1918 at Los Altos (Santa Clara County, California) to two Japanese immigrants (Iyekichi and Chiye) who arrived in the United States in 1915. He had two elder brothers, James, born in 1915 and Kyoshi, born in 1916. Some years later, the family expanded to include William,[1] born in 1931 and Emily, born in 1936.

Takeru Higuchi's childhood is a good example of how his character was moulded by circumstances.

When he was born in Los Altos, his father, Iyekichi, was 33 and his mother, Chiye, was 22. At that time, California was not yet the capital of high technology. It was mainly agricultural, made up of vast estates owned by rich businessmen who employed mainly immigrant workers, most of whom were from Asia. The climate was ideal for large orchards, renowned for plums, apricots and almonds, not to mention raspberries and strawberries. If California was a paradise for fruit trees, it was less so for those who cultivated them and worked on them with their bare hands. Takeru's parents, Iyekichi and Chive quickly realized this in their daily lives: his father tending plum trees and drying the fruit and his mother as a housewife with three young children. From Los Altos, they moved first to Los Gatos then to Mountain View followed by San José, but their life style remained the same: a simple one based around long working days. Takeru and his brother learnt to respect the value of hard work. Their parents, like many first-generation immigrants, they were forced to sacrifice their talents and limit their horizons to the immediate task of providing a living for the family.

To summarize, Takeru Higuchi's childhood was modest but character-forming and left him with a number of essential values: humility, tenacity, honesty, fidelity, curiosity and generosity.

Being admitted to university in 1939 was Takeru Higuchi's first success. After an AB with Honours in Chemistry at the University of California at Berkeley, he was awarded a fellowship from the American government to do a Ph.D. in Physical Chemistry at the University of Wisconsin (Madison). At that time, Madison was a small friendly farming community and its university was rich in promise: a wide range of different courses, many cultural and sporting activities and high-quality research.

Takeru Higuchi joined the laboratory of Professor John E. Willard (1908–1996). Professor Valentino J. Stella, who succeeded Takeru Higuchi at the University of Kansas, said that Prof. Willard was a wise and well regarded mentor (Riley and Rytting, 1991). In 1943, Takeru Higuchi was awarded his Ph.D. after defending a thesis entitled "Photoactivation of bromine solutions". He remained at the University of Wisconsin for post-doctoral studies before taking up a research post at the University of Akron (Ohio). As well as his studies and his thesis, Takeru Higuchi's years in Madison from 1939 to 1943 included a number of significant events.

In 1939, the year that he arrived in the University, he had an encounter which would have repercussions for his future career, with a pharmacy student, Joseph Vincent Swintosky.[2] The two students lived in the same hall and belonged to the same small

[1] Everyone knows the brilliant career of Professor William Higuchi. Professor first at the University of Wisconsin then at Michigan and then at Utah where he is today Emeritus Professor, William Higuchi is known worldwide for his work on a variety of subjects: mass transport, physical chemistry of surfaces and colloids, intestinal and transcutaneous absorption, dissolution of enamel during dental caries. His name is particularly associated with the "*physical approach*" which he used to good effect to study the transport of drugs across the intestinal and cutaneous barriers.

[2] After his Ph.D. defence (1948), after holding a post of Professor at the School of Pharmacy of the University of Wisconsin, J.V. Swintosky moved to industry (SKF) then finished his career in 1987 as Dean of the School of Pharmacy of the University of Kentucky.

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doi:10.1016/j.ijpharm.2011.05.019

group of friends. They were all affected by the difficult climate of the times (financial crash, war in Europe), they all recognized how lucky they were to be in higher education, they were all conscious of the professional and social responsibilities that awaited them and consequently worked conscientiously at their studies. Many of their discussions centred on their respective studies and they were particularly interested in the pharmacy courses that J.V. Swintosky was taking. Takeru Higuchi was not slow to offer his opinion, and pointed out the deficiencies in the programme in several areas: mathematics, physical chemistry and thermodynamics. J.V. Swintosky remembered this some years later.

1941 saw the raid on Pearl Harbour and the declaration of war between Japan and the United States, leading to a dramatic event in Takeru Higuchi's life. Like 120 000 other Japanese and Americans of Japanese extraction, Takeru Higuchi's family were interned at Heart Mountain. This was an extremely painful experience but it did not shake the confidence of either Takeru Higuchi or of his family or of the majority of those interned in the United States (an example of the importance of hoping for a better future for the integration of an immigrant in his adopted country).

In 1943 Takeru Higuchi not only defended his thesis but also married Aya Toki, a girl who, like himself, had been born to Japanese immigrants and who had received a Ph.D. (in Library Science) from the University of Wisconsin, and took up a research post at the University of Akron in Ohio. At the same time, Joseph Vincent Swintosky was hospitalized with tuberculosis and did not return to the University until 1945.

When he left hospital, J.V. Swintosky chose to do his thesis work on the specific surface areas of powders and of pharmaceutical tablets under the direction of Professor L. Busse. He was rapidly confronted by the limitations of his training in physical chemistry and, remembering the comments of his roommates, he pestered the Dean to appoint a staff member in this field. His request was finally heard; at his suggestion, Takeru Higuchi was quickly recruited, in 1947, as Professor of Physical Pharmacy, at the School of Pharmacy in the University of Wisconsin.

Thereafter, events moved rapidly. On the teaching side, courses in mathematics and physical chemistry were gradually introduced. On the research side, the School of Pharmacy at the University of Wisconsin rapidly became a model for other schools of pharmacy in the United States and throughout the world. Many scientists of different nationalities came to the laboratory to complete their training under Professor Takeru Higuchi and, in the words of J.V. Swintosky, the School of Pharmacy in Wisconsin became the Mecca of schools of pharmacy.

During the twenty years spent at the University of Wisconsin, Takeru Higuchi devoted most of his research to fundamental subjects: analytical chemistry (volumetry, chromatography, liquid–liquid extraction), drug instability and reaction kinetics (hydrolysis, oxido-reduction, racemisation, acylation, chlorine transfer), equilibria and thermodynamics (compression, dispersed systems, dissolution, complexation, mass transport, structure–activity relationships). In 1961, Takeru Higuchi published his famous work on the release of active agents from matrix systems. He proposed the equation that bears his name to describe the release from systems with a planar surface. In total, Takeru Higuchi's research at the University of Wisconsin yielded 185 publications.

Professor Higuchi's leaving the University of Wisconsin for the University of Kansas was a difficult moment for the School of Pharmacy of the first[3] and a godsend for the second.

[3] Since this time, the School of Pharmacy of the University of Wisconsin has definitely recovered its prestige in the research field.

The University of Kansas gave him the means to pursue his basic research and, furthermore, allowed to him to use his great talent as an entrepreneur. He was responsible for the creation or development of a number of academic and industrial structures:

- The Department of *Pharmaceutical Chemistry* which Takeru Higuchi headed until1983 and is now one of the top research centres in the domain of medicaments.
- The *Center for Bioanalytical Research* (CBAR) intended to promote the transfer of technology based on discoveries in the university. After merging with other structures, the whole is now known as *Higuchi Biosciences Center* (HBC).
- The Oread laboratory created at the same time as the CBAR.
- The Inter X laboratory devoted to research into pro-drugs.
- The setting-up of a very fruitful collaboration with the Alza Corporation, leading to the development of osmotic systems.

As well as this remarkable research into pro-drugs and osmotic systems, in Kansas, Takeru Higuchi also performed research into routes of administration (oral, transcutaneous, rectal) and on systems based on poly (ortho-esters). It is coincidental that in twenty years at the University of Kansas, he published almost exactly the same number of papers as in the twenty preceding years at the University of Wisconsin: 181 compared to 187.

In 1987 Takeru Higuchi's career was unfortunately cut short by his sudden death. He was taken ill while participating in the event that bears his name (*Higuchi Research Seminar*); he was taken to hospital and died on March 24th

At his funeral, the Senate and House of Representatives of Kansas issued a joint communiqué in homage to Takeru Higuchi, in these words:

> *Dr Higuchi embodied the finest academic traditions, the personal integrity and professional achievement and the deepest commitment to his university, community and state. Dr Higuchi has been referred to as one of the great figures in the history of the University of Kansas and as a teacher, scholar, entrepreneur and benefactor he leaves an indelible mark on the university. Over the past 20 years, it is doubtful if anyone has contributed more than Dr Higuchi did to heighten the international respect for and the prestige of the University of Kansas and left a greater legacy.*

The scientific work of Takeru Higuchi is particularly extensive and represents a turning-point for research in the pharmaceutical sciences. Without doubt, after the 1940s Takeru Higuchi was responsible for opening the way to more rational research on a solid scientific basis in several fields of pharmacy. This work is reflected in almost 400 publications and 80 patents and has been recognized by a large number of awards including the Kolthof Gold Medal Award in Analytical Chemistry in 1977 and the Remington Honor Medal in 1983.

Table 1 summarizes the quantity and diversity of the research carried out by Takeru Higuchi and his collaborators. Few scientists can boast of work ranging from analytical methodology to drug delivery systems by way of various basic studies on reaction kinetics and different aspects of thermodynamics.

Without being exhaustive, Table 2 lists the breakthroughs (new approaches and concepts, new laws, innovations and discoveries) that can be attributed to Takeru Higuchi. These include two indisputable successes:

- The use of a osmotic phenomenon to develop, in collaboration with the Alza Corporation, osmotic systems right up to their appearance on the market.
- The study of various matrix systems and the development, through the study of homogeneous systems with planar surfaces to the so-called "square root" law which now bears his name.

Table 1
Quantity and diversity of the research carried out by Takeru Higuchi.

Field	Specific subjects
Analytical methods	Volumetry, chromatography [column, gas phase, high-performance liquid (HPLC)], liquid–liquid extraction, electrochemistry, various other methods.
Drug stability, reaction kinetics	Hydrolysis, oxido-reduction, racemisation, acylation, chlorine transfer.
Equilibria and thermodynamics	Adsorption, permeation, division, compression, dispersed systems, complexation, dissolution and solubility, quantitative structure–activity relationships (QSARs).
Drug delivery systems (DDS)	Oral route, transcutaneous route, rectal route, pro-drugs, systems based on poly (ortho-ester)s.

Table 2
Examples of breakthroughs made by Takeru Higuchi.

Pharmaceutical subjects	Breakthrough
Acidimetry in non aqueous media	Experimental distinction of the two protons of sulphuric acid
Dissolution of solids	Suggestion of original mathematic models
Structure and stability of pharmaceutical complexes	Development of an original study method known as "Phase Solubility Technique"
Structure–activity relationships for drugs	Invention of the factor "F" to demonstrating the effect of a substitution on the lipophilic nature of a drug
Pro-drugs	Suggestion of N methyl pyridinium-8-carbaldoxime (2-PAM) as an original redox-type system to improve the half-life and passage through the blood–brain barrier
Organochlorinated disinfectants	Proposition of the concept of pKep allowed the ability of substances to generate hypochlorous acid to be compared
Ointments to protect against toxic gases	Evaluation using an original constant called the permeability constant
New forms for drug administration	Invention of osmotic systems. Development of a controlled release polymer system using a substance with "delayed acidity" (anhydride)
Release of drugs from matrix systems	Formulation of the Higuchi (or square-root) equation
Degradation of drugs	A kinetic approach to oxidative and hydrolytic phenomena

The contribution of Takeru Higuchi to the profession as a whole is perhaps less well known than his scientific work but it is no less important.

By his competence as a physical chemist, Takeru Higuchi undoubtedly brought a new direction to pharmaceutical research by moving away from an empirical approach to one based on recent basic concepts, whatever the field. Furthermore, he strove to alert researchers to the close link between basic and applied research and to the importance that should be attached to human relationships in the laboratory.

On this last point, Joseph Vincent Swintosky tells how Takeru Higuchi put several chairs lit by a lamp near his office, which were permanently occupied by students waiting to see their teacher. He also reminds us that he endowed four annual grants of 10 000 dollars each that are awarded to deserving researchers in Kansas and are now named after Takeru Higuchi and his wife Aya.

As far as his contribution to teaching in pharmacy is concerned, Takeru Higuchi brought it the elements that were lacking from the programme in mathematics, physical chemistry and physics. He was particularly aware of the need to share knowledge and therefore was active in creating exchanges between university staff and industry. He can be considered as a pioneer of continuing education.

In industrial practice, Takeru Higuchi brought some useful technical innovations and was behind extensive changes of the activity of pharmaceutical technology laboratories. Among his technical contributions, it is worth citing the use of energy measurements during the formulation of tablets. One of the changes in pharmaceutical technological that should be stressed is the importance that laboratories now give, during preformulation studies, to the determination of the physic-chemical properties of a new active molecule and the search for the physic-chemical environment best adapted for its stability and activity. The work of Takeru Higuchi made a great contribution to these changes.

Within the American pharmaceutical institutions, Takeru Higuchi was one of those who fought for a more open-minded outlook and priority always being given to the improvement of health. With some other colleagues, he was involved in the development of the different associations: the *American Pharmaceutical Association* (APh A) and the *American Association of Pharmaceutical Scientists* (AAPS).

Although a great scientist, Takeru Higuchi was first and foremost a man. His message to all of us would be "*during your life achieve something, however small, for the good of humanity*". This is another way of saying "*one small step for a man, one giant leap for mankind*". For pharmacy, and in particular for pharmaceutical research, Takeru Higuchi allowed a giant leap to be made.

Further reading

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3 May 2011
Available online 26 May 2011