

Honorary Member, Michihito Takahashi, M.D., Ph.D., 1937-2022



Obituary for the Late Dr. Michihito Takahashi

Dr. Michihito Takahashi, an honorary member of the Japanese Society of Toxicologic Pathology, passed away on July 1, 2022 at the age of 84. I am a former colleague who received his guidance, and I wish to express my deep appreciation for his guidance and mentorship during his lifetime and offer my sincere condolences to his family.

Dr. Takahashi graduated from Nagoya City University Medical School in March 1964, and began his career in research as a research associate at the First Department of Pathology of the Nagoya City University Medical School in February 1965. The results of his research on rat gastric carcinogenesis models were widely presented at international conferences and published in many scientific journals at the time. In December 1970, he became a lecturer at the First Department of Pathology of the Nagoya City University Medical School. Starting in April 1975, he worked as an assistant professor at the Eppley Institute for Cancer Research, University of

Nebraska Medical Center in the United States for two years, focusing on hamster pancreatic carcinogenesis research. Then, in April 1978, he was invited to be the section chief of the Department of Pathology in the newly established Biological Safety Research Center, National Institute of Hygienic Sciences. He was promoted to be the head of the Department of Pathology in April 1991. He continued to serve as the head of the Department of Pathology, National Institute of Health Sciences, as it was renamed in July 1997, and retired when he reached the mandatory retirement age in March 1998. After retirement, he was engaged in post-graduate education in the Department of Pathophysiology as professor in the School of Pharmacy at Showa University. He also simultaneously established the Pathology Peer Review Center and devoted himself to ensuring the appropriateness and reliability of the application documentation in the field of pathological diagnostics. I heard that he continued working at the center, even just before his death, so I imagine that his death must have been a very unexpected event for him.

As the section chief and head of the Department of Pathology, National Institute of Hygienic Sciences, he was widely involved in carcinogenicity testing and evaluation of various chemical substances including pharmaceuticals, food additives, and pesticides. The results of his work have been published in many international journals, and I need not repeat the details. He was also a member of various committees including the Central Pharmaceutical Affairs Council, the Food Sanitation Investigation Council, and the Living Environment Council, and made significant contributions to the Ministry of Health, Labour and Welfare over many years. He also dedicated himself to the development of guidelines for various toxicity testing methods at the Organization for Economic Cooperation and Development (OECD) and the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH; International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use since 2015). In addition to this regulatory work, he also made particularly significant contributions in carcinogenesis research. Using rat two-step gastric carcinogenesis models, he published his findings that a high-salt diet and gastric acid secretion stimulants promote gastric carcinogenesis in international journals. He also used hamster two-step pancreatic carcinogenesis models to continue studies on the pathogenesis of pancreatic cancer, which remains the most common cause of cancer mortality today. Since October 1991, I have been involved in the research on rat gastric carcinogenesis and hamster pancreatic carcinogenesis as a section chief of the Pathology Department at the National Institute of Health Sciences under the guidance of Dr. Takahashi. I am deeply grateful for the truly fulfilling research life I was able to spend working with him. He established the details of the systematic long-term animal testing methods for evaluating carcinogenicity from an administrative standpoint. These are reflected in the "Guidelines for Toxicity Studies of Pharmaceuticals (Pharmaceutical Affairs Bureau, Ministry of Health and Welfare)". It is also worth mentioning that he served as general supervisor for translation of the book "Casarett & Doull's Toxicology", the bible of toxicology that many researchers in the field of toxicology always keep at hand.

As those who have known Dr. Takahashi personally can testify, he was a researcher with a great deal of wit. I can still vividly recall his joyful appearance at staff outings and year-end parties during his days at the Department of Pathology, National Institute of Health Sciences, social gatherings of executive staff members of the Safety Center, as well as various academic societies and research groups.

May Dr. Michihito Takahashi's soul rest in peace.

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Akiyoshi Nishikawa

*Honorary member of the Japanese Society of Toxicologic Pathology and
guest researcher at the National Institute of Health Sciences*

My encounter with Dr. Michihito Takahashi and his legacy

After graduating from Nagoya City University Medical School, I joined the First Department of Pathology after a one-year internship at Meijo Hospital. At that time, my professor was Dr. Hisamasa Sato, a former student of Dr. Ryojun Kinoshita of Osaka University, who is famous for his work on hepatic cancer in rats induced by butter yellow. In those days, Dr. Takahashi, who was three years my senior, was a research associate. For me, who joined the department as a research associate, Dr. Takahashi was like a big brother at work. Dr. Takahashi and I were also connected as student researchers in Dr. Sato's Department of Pathology, although there was a time lag between us. I take this opportunity to impart my memories of Dr. Takahashi during my days at Nagoya City University and express my condolences to his family.

I would like to share a story Dr. Takahashi told me around the time when I joined Dr. Sato's Department of Pathology. After graduating from the university and completing a one-year internship at Toyohashi Municipal Hospital, Dr. Takahashi was supposed to join the Department of Obstetrics and Gynecology at Nagoya City University in January 1965. Dr. Takahashi visited Dr. Sato's Department of Pathology to greet him. At the time, one of the research associates in the department had switched to dermatology, and the other one was often absent with illness. The assistant professor sternly told him, "If you don't join the department, who will take care of it?" Dr. Takahashi then changed his mind overnight and decided to join the Department of Pathology.

After joining the Department, Dr. Sato only told him, "I want you to research gastric carcinogenesis. 4-NQO would be a good carcinogen to use. I think that the surface activity of sodium alkylbenzene sulfonic acid soda (ABS) may contribute to carcinogenesis." Dr. Takahashi then began his research activities after receiving this guidance. After testing various experimental conditions, he succeeded in inducing gastric cancer in rats, which resulted in his dissertation and was published in GANN (currently Cancer Science). That is, he succeeded for the first time in developing a model of gastric carcinogenesis, which is pathologically atypical, but occurs infrequently. It was a remarkable achievement. This research later led him to become a member of the Special Cancer Research Group of the Ministry of Education (Dr. Nagayo's group), where he worked on animal gastric carcinogenesis research. It should also be noted that these results were produced in a handmade cage designed by Dr. Takahashi, which I will describe below.

One of my memories of the department I joined where Dr. Takahashi was engaged in research on gastric carcinogenesis, is that I had to make rat-breeding cages by hand like those designed by Dr. Takahashi, in order to start my own animal experiments. Our pathology department was very underfunded. When starting animal experiments, we could not purchase ready-made rat-breeding cages, so we had to make the cages designed by Dr. Takahashi. A hardware store near the university would make the bottom and frame of the cages for us at a bargain price, and we then attached wire mesh and plastic plates using wire and pliers to the frame. In those days, while working on the cage, I remember asking myself foolishly if this was the right way to go about it. However, all of Dr. Takahashi's brilliant achievements mentioned above were born from the first cage he designed himself.

Dr. Takahashi was very enthusiastic in encouraging students visiting the department as student researchers to remain with his department upon their graduation. It is not clear whether this was successful or not, but it provided Drs. Tsuda, Sugiura, Hananouchi, Shirai, Hirose, Tatematsu, and other student researchers with the opportunity to become researchers and graduate students in his department after graduation, and this group promoted the carcinogenesis research of Professor Nobuyuki Ito, who took over after Dr. Sato's retirement. In this way, Dr. Takahashi established a great foundation at the Department of Pathology in terms of human resources.

After Dr. Sato retired, the selection of his successor was postponed for one year for various reasons. I clearly remember that Dr. Takahashi led the Department during that period without a professor and responded appropriately both in- and outside the university. I moved to Nagoya Health University School of Health Sciences (currently Fujita Health University) before Professor Ito succeeded Dr. Sato. Dr. Takahashi, who had become a lecturer, went to the U.S. to study upon the recommendation of Dr. Ito. Sometime after he returned to Japan, he moved to Tokyo for research as requested by Dr. Odajima, the first Head of the Department of Pathology at the National Institute of Hygienic Sciences (currently the National Institute of Health Sciences). Therefore, although I spent only a little over six years working side by side with Dr. Takahashi, it was a very enriching time for me. He taught me many things about research while performing three pathological autopsies a day and making histopathological diagnoses. On the other hand, I am proud that I could teach him as well. Since we both had some free time recently, I enjoyed trips to hot springs with Dr. Takahashi and his wife. Unfortunately, I have to say that we had just started to enjoy such trips shortly before his death. I am very grateful to him for many joyful memories of my youth, now that I am an old man. Rest in peace, Dr. Michihito Takahashi.



In 1966, when he was 29.

With my deepest condolences to his family (Written on July 27, 2022.)

*Shoji Fukushima Association for Promotion of Research
on Risk Assessment*