

In Memoriam: Honorary Member Nobuyuki Ito, MD, PhD, 1928-2010

Recently the scientific world, particularly toxicologic pathology, lost one of its great leaders, Nobuyuki Ito, MD, PhD, who passed away on October 6, 2010 in Nagoya, after nearly 5 years battling illness. He was 81.



In his academic life, Dr. Ito left behind a legacy of leadership and advancement of toxicologic pathology, toxicology, and research on chemical carcinogenesis. He received the 2005 Education Award from the Society of Toxicology celebrating recognition of his lifelong contributions to scientific and professional education. Dr. Ito began his pioneering efforts in toxicology education 35 years ago when he established an extensive teaching and training program for toxicologists at the Department of Pathology, Nagoya City University Medical School. He trained two generations of toxicologists and toxicologic pathologists in Japan and several from other countries, first as Chairman of the Department, then as Dean of the Medical School and lastly as President of the University. Dr. Ito and his students and senior scientists have made significant contributions to risk assessment and regulation of chemicals and food additives in Japan and internationally. His works in the field of histogenesis and modulation of the neoplastic process and on antioxidants in anti-carcinogenesis have been acknowledged by many societies, including the Princess Takamatsu Cancer Research Fund, the Japanese Cancer Association, and the International Federation of Societies of Toxicologic Pathology. During his distinguished career at Nagoya City

University Medical School. Dr. Ito authored and co-authored with his numerous students and associates more than 600 peer-reviewed scientific publications. His former students, numbering more than 100, are in prestigious and important positions around the world, continuing his task of educating toxicologists in Japan, Korea, Thailand, Brazil and the United States.

Born in Kyoto, Dr. Ito graduated from Nara Medical University, Nara, 1952, received his D.Ms. (Ph.D.), 1961, from Osaka University School of Medicine, and began his academic faculty career in 1954. He studied hepatocarcinogenesis from 1962 to 1964 in the laboratory of Professor Emmanuel Farber, University of Pittsburgh. He was very impressed by how well equipped the research facility was and the overwhelming amount of material available at the University of Pittsburgh. His experience in Farber's laboratory very much influenced his fundamental research attitude, direction and system after his return to Japan.

In 1972, he became chairman and professor at the Department of Oncological Pathology, Cancer Center, Nara Medical University, based on his extensive and productive research activities. In 1974, he became chairman and professor of the First Department of Pathology, Nagoya City University Medical School, Nagoya, following Professor Hisamasa Sato who had been his teacher at Nara Medical University. Dr. Ito's research base was anchored to Nagoya thereafter as professor, as Dean and then president of the University and continuing as Emeritus Professor until his unfortunate terminal illness.

His career as a researcher of *in vivo* chemical carcinogenesis and as a pathologist began upon his graduation from Nara Medical University and his significant contributions to carcinogenesis, toxicology, toxicologic pathology and risk assessment cannot be expressed simply by word. He has provided the fundamental research needed for the assessment of numerous synthetic and natural chemicals that are introduced into the environment. He was the first to demonstrate carcinogenic activity of many chemicals, including α -benzenehexachloride (α -BHC; a pesticide), quinoline (industrial chemical), butylated hydroxyanisole (BHA; food additive used as an antioxidant), catechol (a natural antioxidant), 2-amino-1-methyl-6-phenylimidazo [4,5-b] pyridine (PhIP; meat pyrolysate product) and captafol (a pesticide). Best known for his research on one food additive, BHA, this revolutionized the field of carcinogenesis research and led to a consensus within the scientific community that regulatory actions should be decided after thorough examination of both the benefit and risk of the chemicals and utilizing all of the research available about them, not just relying on the outcome of long term rodent bioassays. After his publication of the carcinogenicity of BHA, previously considered as safe and possibly a chemopreventive

agent, heated discussions by many experts from U.S.A, England, Europe, Canada and Japan took place. It was decided not to ban BHA since it is carcinogenic only at very high doses, the carcinogenic target organ in rodents is the forestomach which humans do not have, it is not genotoxic, and it is a very useful food additive antioxidant. His 1983 report on BHA changed the consensus approach regarding risk assessment of carcinogenic substances, particularly non-genotoxic carcinogens. After his pioneering work with BHA, the phrase "before Ito and after Ito" was often used among researchers recognizing this landmark decision. After discovery of BHA carcinogenicity in rats, Ito's group discovered other natural carcinogenic antioxidants present in plants, including catechol, sesamol, caffeic acid, hydroquinone and 4-methoxyphenol. The research on antioxidants was further extended to studies on modification of chemical carcinogenesis by antioxidants and led to the conclusion that the modification by antioxidants depends upon the target organ; an inhibitory effect could occur in one organ but enhancement in other organs.

Dr. Ito also concentrated on developing and improving animal models for the study of cancers of the prostate, urinary bladder, kidney, stomach, intestine and liver. He developed a new in vivo system using male rats which is capable of detecting the carcinogenicity of chemicals in a relatively short time (8 weeks) with high sensitivity and specificity. This system, known as the medium-term liver bioassay system, was approved as an alternative carcinogenicity screening method by the International Conference on Harmonization of Technical Requirements for Regulation of Pharmaceuticals for Human Use (ICH). The system consists of an initial i.p. injection of diethylnitrosamine (DEN) as initiator followed by the administration of the test compound for 6 weeks beginning 2 weeks after the initiation with 2/3 partial hepatectomy on week 3. The development of preneoplastic lesions in the liver is quantitatively analyzed as glutathione S-transferase placental (GST-P) form-positive foci by immunohistochemical visualization. Dr. Ito's group has evaluated 313 chemicals over the past 20 years, with more than 100 publications reporting the data that demonstrate its feasibility and reliability. In addition, he also established a multi-organ carcinogenicity screening system using rats.

Dr. Ito was a superb scientist and mentor, constantly seeking new ideas, and directing, training and mentoring numerous young researchers worldwide.

He had boundless energy and enthusiasm, and provided significant leadership for many scientific societies in Japan and internationally. In Japan, these

included the Japanese Society of Toxicologic Pathology (JSTP), the Japanese Society of Pathology (JSP) and the Japanese Cancer Association (JCA). He served as President of JSTP for 5 years, developing it as a significant professional society. He took charge of office functions and established the management and infrastructure of the society. He served as president of the annual scientific meeting of JSTP in 1987. He was also instrumental in founding the International Federation of Societies of Toxicologic Pathology (IFSTP), and organized its first international conference while he was president in 1992, held in Nagoya. This was but one of the many local, national and international meetings he organized, always memorable for their scientific and social content. He was President of the 52nd Annual Meeting of JCA that was successfully held in Nagoya in 1994. The Japanese Society of Food Chemistry was also one of his major areas of effort, serving as president from 1999 to 2002. He also contributed in significant ways to the Society of Toxicologic Pathology (STP), Society of Toxicology (SOT) and the American Association of Cancer Research in the U.S.A.

Recognized internationally for his scientific contributions, Dr. Ito was named to numerous panels, advisory boards and committees in Japan, in the U.S.A. (Food and Drug Administration and Environmental Protection Agency), and the International Agency for Research on Cancer and WHO/FAO Joint Meeting on Pesticide Residues. He was also chairman of the Food Safety Committee of the Ministry of Health and Welfare, Japan.

Dr. Ito's expertise, contributions, and sustained excellence were recognized with numerous other awards and honors. He received the Award of the Princess Takamatsu Cancer Research Fund (1985, Tokyo), the Chu-nichi Cultural Award (1985, Nagoya), the Robert E. Greenfield Lectureship in Carcinogenesis (1989, Omaha, U.S.A.), Yomiuri Tokai Medical Award (1991, Nagoya), Honorary Doctor of science Degree from University of Nebraska Medical Center (1994, U.S.A.), Medal with Purple Ribbon (1995), the Takeda Prize for Medical Science (1995, Osaka), Honorary Doctor of Science Degree from University of Cagliari (1996, Italy), Tomizo Yoshida Award of JCA (1996, Tokyo), the Kitashi-Mochizuki Memorial Award (2002, Shizuoka), and the Order of the Sacred Treasure, Gold and Silver Star (2003).

Throughout his long and distinguished career, Dr. Ito has touched and developed a tremendous number of scientists in toxicologic pathology, as well as in toxicology, pathology, and carcinogenesis. They and his family made Ito's world, and he will be forever remembered with gratitude, admiration, respect, and friendship.

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